Report on the Deliberation Results

September 12, 2017

Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Darzalex Intravenous Infusion 100 mg, Darzalex Intravenous Infusion 400 mg
Non-proprietary Name	Daratumumab (Genetical Recombination) (JAN*)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	December 20, 2016

Results of Deliberation

In its meeting held on September 8, 2017, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product. The re-examination period is 10 years. Both the drug product and its drug substance are classified as a powerful drugs.

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because Japanese data from clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey on all patients until data from a certain number of patients are collected in identifying the characteristics of patients treated with the product, collect data on the safety and efficacy of the product without delay, and take necessary action for the proper use of the drug product.

**Japanese Accepted Name (modified INN)*

Review Report

August 30, 2017
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Darzalex Intravenous Infusion 100 mg, Darzalex Intravenous Infusion 400 mg
Non-proprietary Name	Daratumumab (Genetical Recombination)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	December 20, 2016
Dosage Form/Strength	Darzalex solution for injection containing 100 or 400 mg of daratumumab (genetical recombination) per vial (5 or 20 mL)
Application classification	Prescription drug, (1) Drug with a new active ingredient
Definition	Daratumumab is a recombinant human IgG1 monoclonal antibody against human CD38. Daratumumab is produced in Chinese hamster ovary cells. Daratumumab is a glycoprotein (molecular weight: ca. 148,000) composed of 2 H-chains (γ1-chains) consisting of 452 amino acid residues each and 2 L-chains (κ-chains) consisting of 214 amino acid residues each.

Structure

Amino acid sequence:

L-chain

EIVLTQSPAT LSLSPGERAT LSCRASQSVS SYLAWYQQKP GQAPRLLIYD

ASNRATGIPA RFSGSGSGTD FTLTISSLEP EDFAVYYCQQ RSNWPPTFGQ

GTKVEIKRTV AAPSVFIFPP SDEQLKSGTA SVVCLLNNFY PREAKVQWKV

DNALQSGNSQ ESVTEQDSKD STYSLSSTLT LSKADYEKHK VYACEVTHQG

LSSPVTKSFN RGEC

H-chain

EVQLLESGGG LVQPGGSLRL SCAVSGFTFN SFAMSWVRQA PGKGLEWVSA

ISGSGGGTYY ADSVKGRFTI SRDNSKNTLY LQMNSLRAED TAVYFCAKDK

ILWFGEPVFD YWGQGTLVTV SSASTKGPSV FPLAPSSKST SGGTAALGCL

VKDYFPEPVT VSWNSGALTS GVHTFPAVLQ SSGLYSLSSV VTVPSSSLGT

QTYICNVNHK PSNTKVDKRV EPKSCDKTHT CPPCPAPELL GGPSVFLFPP

KPKDTLMISR TPEVTCVVVD VSHEDPEVKF NWYVDGVEVH NAKTKPREEQ

YNSTYRVVSV LTVLHQDWLN GKEYKCKVSN KALPAPIEKT ISKAKGQPRE

PQVYTLPPSR EEMTKNQVSL TCLVKGFYPS DIAVEWESNG QPENNYKTTP

PVLDSDGSFF LYSKLTVDKS RWQQGNVFSC SVMHEALHNH YTQKSLSLSP

GK

Intra-chain disulfide bonds: solid lines

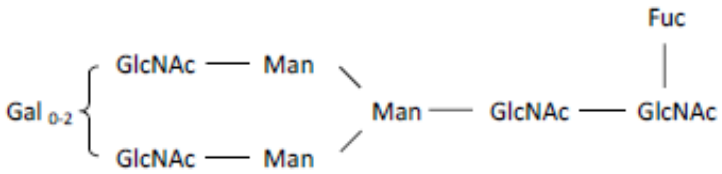
Inter-chain disulfide bonds: L-chain C214-H-chain C225, H-chain C231-H-chain C231, H-chain C234-H-chain C234

Pyroglutamic acid (partial): H-chain E1

Glycosylation site: H-chain N302

Partial processing: H-chain K452

Main proposed carbohydrate structure



Gal, galactose; GlcNAc, *N*-acetylglucosamine; Man, mannose; Fuc, fucose.

Molecular formula: $C_{6466}H_{9996}N_{1724}O_{2010}S_{42}$ (for the protein)
Molecular weight: ca. 148,000

Items Warranting Special Mention
Orphan drug (Orphan Drug Designation No. 393 of 2016 [28 *yaku*]; PSEHB/PED Notification No. 1205-3 dated December 5, 2016, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)
Reviewing Office Office of New Drug V

Results of Review
On the basis of the data submitted, PMDA has concluded that the product has efficacy in the treatment of relapsed or refractory multiple myeloma, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. The infusion reactions, bone marrow depression, infections, haemolysis, and tumour lysis syndrome should be further evaluated in the postmarketing setting.

Indication
Relapsed or refractory multiple myeloma

Dosage and Administration
The usual adult dose is 16 mg/kg of daratumumab (genetical recombination) administered as an intravenous drip infusion according to the following dosing schedule:
In combination with lenalidomide and dexamethasone,
Weekly (Weeks 1-8), every 2 weeks (Weeks 9-24), and every 4 weeks (Week 25 onwards).
In combination with bortezomib and dexamethasone,
Weekly (Weeks 1-9), every 3 weeks (Weeks 10-24), and every 4 weeks (Week 25 onwards).

Conditions of Approval
1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because Japanese data from clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey on all patients until data from a certain number of patients are collected in identifying the characteristics of patients treated with the product, collect data on the safety and efficacy of the product without delay, and take necessary action for the proper use of the drug product.

Attachment

Review Report (1)

June 27, 2017

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Darzalex Intravenous Infusion 100 mg, Darzalex Intravenous Infusion 400 mg
Non-proprietary Name	Daratumumab (Genetical Recombination)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	December 20, 2016
Dosage Form/Strength	Darzalex solution for injection containing 100 or 400 mg of daratumumab (genetical recombination) per vial (5 or 20 mL)
Proposed Indication	Relapsed or refractory multiple myeloma
Proposed Dosage and Administration	The usual adult dose is 16 mg/kg of daratumumab (genetical recombination) administered as an intravenous drip infusion according to Method A or Method B. Method A: Duration of treatment/treatment interval Weeks 1 to 8/weekly (total of 8 doses) Weeks 9 to 24[1)]/every 2 weeks (total of 8 doses) Week 25 onwards [2), 3)]/every 4 weeks [1)] First dose of the every-2-week dosing schedule is given at Week 9. [2)] First dose of the every-4-week dosing schedule is given at Week 25. [3)] Treatment from Week 25 onwards is continued until disease progression. Method B: Duration of treatment/treatment interval Weeks 1 to 9/weekly (total of 9 doses) Weeks 10 to 24[1)]/every 3 weeks (total of 5 doses) Week 25 onwards[2), 3)]/every 4 weeks [1)] First dose of the every-3-week dosing schedule is given at Week 10. [2)] First dose of the every-4-week dosing schedule is given at Week 25. [3)] Treatment from Week 25 onwards is continued until disease progression.

Table of Contents

List of Abbreviations

ADCC	antibody dependent cell mediated cytotoxicity
ADCP	antibody dependent cellular phagocytosis
ADP	adenosine diphosphate
ADPR	adenosine diphosphate ribose
AEX	anion exchange chromatography
ALT	alanine aminotransferase
application	application for marketing approval
APTT	activated partial thromboplastin time
AST	aspartate aminotransferase
ATP	adenosine triphosphate
Bd	combination therapy of bortezomib and dexamethasone
BMP	combination therapy of bortezomib, melphalan, and prednisone (prednisone is unapproved in Japan)
BTd	combination therapy of bortezomib, thalidomide, and dexamethasone
BTZ	bortezomib
cADPR	cyclic adenosine diphosphate ribose
CAL	cells at the limit of *in vitro* cell age
CDC	complement dependent cytotoxicity
CEX	cation exchange chromatography
cGDPR	cyclic guanosine diphosphate ribose
CHO cells	Chinese hamster ovary cells
CI	confidence interval
cIEF	capillary isoelectric focusing
CMV	cytomegalovirus
CQA	critical quality attributes
CR	complete response
CrCL	creatinine clearance
CRP	C reactive protein
cSDS	capillary electrophoresis sodium dodecyl sulfate
daratumumab	daratumumab (genetical recombination)
daratumumab/Bd	combination therapy of daratumumab and Bd
daratumumab/Ld	combination therapy of daratumumab and Ld
DEX	dexamethasone
DIRA	daratumumab-specific immunofixation reflex assay

DLT	dose limiting toxicity
DNA	deoxyribonucleic acid
DTT	dithiothreitol
ECL	electrochemiluminescence
ECOG	Eastern Cooperative Oncology Group
EC_{50}	50% effective concentration
ELISA	enzyme-linked immunosorbent assay
$F(ab')_2$	antigen-binding fragment that includes a hinge region
Fc	fragment crystallizable
FcRn	neonatal Fc receptor
FITC	fluorescein isothiocyanate
GGT	γ-glutamyltransferase
[redacted]	[redacted]
HBV	hepatitis B virus
HCP	host cell protein
hERG	human *ether-a-go-go* related gene
His	histidine
HRP	horseradish peroxidase
IDMC	independent data monitoring committee
IFN-γ	interferon-γ
Ig	immunoglobulin
IHC	immunohistochemistry
IL-1β	interleukin-1β
IL-6	interleukin-6
IMWG	International Myeloma Working Group
IMWG Criteria	criteria developed by the IMWG
IRC	independent review committee
ISS	international staging system
ITT	intent-to-treat
K_D	dissociation constant
KLH	keyhole limpet hemocyanin
Ld	combination of lenalidomide and dexamethasone
LD	combination of lenalidomide and high-dose dexamethasone
LDH	lactate dehydrogenase
lenalidomide	lenalidomide hydrate
Lys	lysine
MCB	master cell bank
MedDRA	Medical Dictionary for Regulatory Activities
MedDRA/J	Medical Dictionary for Regulatory Activities Japanese version
MM	multiple myeloma
MMV	murine minute virus
[redacted]	[redacted]
MR	minimal response
MTD	maximum tolerated dose
NCCN	National Comprehensive Cancer Network
NCCN guidelines	National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology, Multiple Myeloma
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NCI-PDQ	National Cancer Institute Physician Data Query Multiple Myeloma and Other Plasma Cell Neoplasms
NE	not estimable
OS	overall survival
PBMC	peripheral blood mononuclear cell

PD	progressive disease
Pd	combination therapy of pomalidomide and DEX
PFS	progression-free survival
PK	pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetics
PRV	pseudorabies virus
PS	performance status
PT	preferred term
QbD	quality by design
QD	quaque die (once a day)
QTcF	QT interval corrected using Fridericia's formula
ΔQTcF	changes from baseline in QTcF
QW	quaque 1 week (once every week)
Q2W	quaque 2 weeks (once every 2 weeks)
Q3W	quaque 3 weeks (once every 3 weeks)
Q4W	quaque 4 weeks (once every 4 weeks)
REO	reovirus
SCID mouse	severe combined immunodeficient mouse
SCID-beige mouse	severe combined immunodeficient-beige mouse
sCR	stringent complete response
SD	stable disease
SEC	size exclusion chromatography
SMQ	standard MedDRA queries
SOC	system organ class
SPR	surface plasmon resonance
Study 1001	Study 54767414MMY1001
Study 1002	Study 54767414MMY1002
Study 1005	Study 54767414MMY1005
Study 2002	Study 54767414MMY2002
Study 3003	Study 54767414MMY3003
Study 3004	Study 54767414MMY3004
TNF-α	tumor necrosis factor α
[redacted]	[redacted]
VGPR	very good partial response
V_1	central volume of distribution
WCB	working cell bank
X-MuLV	xenotropic murine leukemia viruses
7-AAD	7-amino actinomycin D

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

1.1 Outline of the product proposed product

Daratumumab is a humanized anti-CD38 immunoglobulin G1 (IgG1) monoclonal antibody discovered by Genmab (Denmark).

Daratumumab is considered to bind to the CD38 expressed on the surface of multiple myeloma (MM) cells and induce complement dependent cytotoxicity (CDC), antibody dependent cellular phagocytosis (ADCP), and antibody dependent cell mediated cytotoxicity (ADCC) in MM cells, thereby inhibiting tumor proliferation.

1.2 Development history etc.

Outside Japan, a phase I/II study (Study GEN501) of daratumumab monotherapy in patients with relapsed or refractory MM was started by Genmab (Denmark) in March 2008. Later in September 2013, a foreign phase II study (Study 2002) of daratumumab monotherapy in patients with relapsed or refectory MM was started by the Janssen Research & Development, LLC (US). A global phase III study (Study 3003) of daratumumab/lenalidomide and dexamethasone (Ld) therapy and a foreign phase III study (Study 3004) of daratumumab/bortezomib and dexamethasone (Bd) therapy were started in June 2014 and September 2014, respectively, both in patients with relapsed or refractory MM.

In the US and EU, data including the pivotal data from Study 2002 were submitted in an application for the marketing approval of daratumumab monotherapy in July 2015 in the US and in September 2015 in the EU. In the US, daratumumab was approved for the following indication in November 2015: “DARZALEX is a human CD38-directed monoclonal antibody indicated for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent.” In EU in May 2016, daratumumab was approved for the following indication: “DARZALEX as monotherapy is indicated for the treatment of adult patients with relapsed or refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.” In addition, data including pivotal data from Studies 3003 and 3004 were submitted in an application for marketing approval of daratumumab in combination with other drugs, e.g., Ld and Bd in the US and EU in August 2016. In the US, the combination therapy of daratumumab was approved for the following indication in November 2016: “DARZALEX is a CD38-directed cytolytic antibody indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with multiple myeloma who have received at least one prior therapy” and “DARZALEX is a CD38-directed cytolytic antibody indicated in combination with pomalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least two prior therapies including lenalidomide and a proteasome inhibitor” in June 2017. In the EU, the combination therapy of daratumumab was approved for the following indication in April 2017: “DARZALEX is

indicated in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least one prior therapy."

As of May 2017, daratumumab has been approved for the indication of MM in 45 countries and regions.

In Japan, a phase I study of daratumumab monotherapy (Study 1002) and a phase Ib study of daratumumab/Bd (Study 1005) were started by the applicant in patients with relapsed or refractory MM in April 2014 and August 2015, respectively. Enrollment of patients in Study 3003 mentioned above was started in [redacted].

Data including pivotal data from Studies 3003 and 3004 were submitted in an application for marketing approval of daratumumab.

Daratumumab was designated as an orphan drug with a proposed indication for the treatment of "relapsed or refractory multiple myeloma" in December 2016 (Orphan Drug Designation No. 393 of 2016 [28 *yaku*]).

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

2.1 Drug substance

2.1.1 Generation and control of cell substrate

Transgenic mice expressing human IgG were immunized with [redacted]-labeled human CD38 for which human CD38 expressing [redacted] cells are bound to [redacted], and hybridoma cells were generated by fusing mouse myeloma cells to the obtained [redacted]. Clones expressing anti-CD38 antibodies were isolated from the hybridoma cells. Gene fragments encoding the variable region of human IgG1 heavy and light chains were prepared from the base sequence of the hybridoma clone and were then inserted into a plasmid containing the constant region of human IgG1 heavy and light chains, and the expression construct for heavy and light chains of daratumumab was generated, respectively. The expression construct for daratumumab was produced by using the gene fragments expressing the heavy and light chains for the 2 constructs. The expression construct for daratumumab was then transfected in the Chinese hamster ovary (CHO) cells. The most appropriate clone for production of daratumumab was chosen from the obtained cell line and was used to prepare the master cell bank (MCB) and working cell bank (WCB).

The MCB, WCB, and cells at the limit of in vitro cell age (CAL) have been tested for identity and purity in accordance with ICH Q5A(R1), Q5B, and Q5D guidelines and were confirmed to be genetically stable during the manufacturing process. Adventitious viruses or non-viral adventitious agents, except for endogenous retrovirus-like particles that are commonly observed in rodent cell lines, were undetected within the range of parameters tested.

The MCB and WCB are stored in the vapor phase of liquid nitrogen. No new MCB is planned to be prepared, but a new WCB will be prepared as appropriate.

2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of the following steps: preculture, expanded culture, production culture, clarification, [redacted] chromatography, virus inactivation [redacted] and [redacted], concentration and freezing, thawing and pooling, cation exchange chromatography (CEX), anion exchange chromatography (AEX), viral removal filtration, concentration and [redacted], and preparation, aliquoting, freezing, testing, and storage of the drug substance. The manufactured drug substance is stored in [redacted] containers at [redacted]°C.

Among the above, the steps [redacted] are defined as critical steps.

Process validation was performed at the commercial scale to validate the manufacturing process for the drug substance.

2.1.3 Safety evaluation of adventitious agents

Except for the CHO cells used as the host cells, no animal- or human-derived raw materials are used in the manufacturing process of the drug substance.

MCB, WCB, and CAL have been tested for purity [see Section 2.1.1]. Pre-harvest unprocessed bulk at commercial scale was tested for microorganisms, mycoplasma, and *in vitro* adventitious viruses. None of the tests revealed contamination with viral or non-viral adventitious agents within the range of the parameters tested. Tests for microorganisms, mycoplasma, and *in vitro* adventitious viruses are included as in-process control tests for unprocessed bulk.

Viral clearance studies of the purification process were performed with model viruses. The results demonstrated a certain robustness of the purification process (Table 1).

Table 1. Results of viral clearance studies

Manufacturing process	Viral reduction factor (log_{10})			
	X-MuLV	MMV	PRV	REO
[redacted] chromatography	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] virus inactivation and [redacted]	[redacted]	[redacted]	[redacted]	[redacted]
AEX	[redacted]	[redacted]	[redacted]	[redacted]
Viral removal filtration	[redacted]	[redacted]	[redacted]	[redacted]
Overall virus reduction factor	>16.7	9.6	>15.2*	>9.2*

*: [redacted]

2.1.4 Manufacturing process development

The following are major changes made to the drug substance manufacturing process during development (Process 1, Process 2, Process 3, and the proposed commercial process).

- Process 1 → Process 2: change in [redacted], changes in [redacted] and [redacted], etc.
- Process 2 → Process 3: changes in [redacted] for [redacted], [redacted] of drug substance, and the [redacted] in [redacted] step
- Process 3 → proposed commercial process: change in [redacted], etc. used in the [redacted] step.

The drug product for phase I/II studies produced from the drug substance manufactured by Process [redacted] was used in phase I/II studies, and the drug product for phase III studies produced from the drug substance manufactured by Processes [redacted] and [redacted] was used in phase III studies [see Section 6.1.2]. For all process changes, comparability of quality attributes was evaluated, and the comparability of drug substances between pre-change and post-change has been demonstrated.

A quality by design (QbD) approach was used to develop the manufacturing process [see Section 2.3].

2.1.5 Characterization

2.1.5.1 Structure and properties

Characterization was performed as shown in Table 2.

Table 2. Attributes evaluated in characterization

Primary structure	Amino acid sequence, post-translational modification (cyclization of N-terminal, glycation, oxidation, isomerization, deletion of C-terminal lysine residue)
Higher-order structure	Secondary structure, higher-order structure, disulfide bond, free thiol group
Physicochemical properties	Molecular weight, molecular variants
Carbohydrate structure	Structure of N-linked oligosaccharide, neutral monosaccharide composition analysis
Biological activity	CD38-binding activity
	[redacted] activity ([redacted], [redacted], [redacted])
	ADCC activity, CDC activity

CD38-binding activity of daratumumab was confirmed by [redacted]. Daratumumab binding to [redacted] was evaluated by [redacted], and a high affinity to [redacted], which is a characteristic of IgG1, was confirmed. ADCC activity was evaluated by [redacted] that measures [redacted] due to [redacted] expression in a system that uses [redacted] expression-confirmed [redacted] cells as target cells and [redacted]-expressing [redacted] cells as [redacted] cells, in which the [redacted] was introduced as a [redacted]. CDC activity was evaluated by reacting target [redacted] cells with [redacted] together with daratumumab, and by measuring [redacted] produced by cell lysis using a [redacted] that [redacted]. Dose-dependent ADCC and CDC activities were confirmed for daratumumab.

2.1.5.2 Product-related substances and product-related impurities

Based on results of the analyses shown in Section "2.1.5.1 Structure and characteristics," glycated, oxidized, aggregated, cleaved, and deamidated forms were identified as product-related impurities. The

product-related impurities have been properly controlled with the drug substance and drug product specifications (glycated form, [redacted]; oxidized form, [redacted]; aggregated form, [redacted] and [redacted]; cleaved form, [redacted] and [redacted]; and deamidated form, [redacted]).

2.1.5.3 Process-related impurities

HCP, host cell DNA, [redacted], [redacted], [redacted], [redacted] and [redacted] were identified as process-related impurities. The manufacturing process have been demonstrated to effectively remove all the process-related impurities.

2.1.6 Control of drug substance

The proposed specification for the drug substance consists of content, description, identification (dot-blot, peptide map), pH, purity (capillary electrophoresis sodium dodecyl sulfate [cSDS] [reducing and non-reducing], size exclusion chromatography [SEC]), oligosaccharide analysis, charge inhomogeneity (capillary isoelectric focusing [cIEF]), microbial limits, bacterial endotoxins, biological activities (ADCC and CDC activities), and assay (ultraviolet-visible absorption spectrophotometry).

2.1.7 Stability of drug substance

Main stability studies of the drug substance are shown in Table 3.

Table 3. Outline of main stability studies of the drug substance

	No. of batches*1	Storage condition	Study period	Storage package
Long-term testing	4	[redacted] ± [redacted]°C	[redacted] months*2	[redacted] container
Accelerated testing	4	[redacted] ± [redacted]°C	[redacted] months	
Stress testing	4	[redacted] ± [redacted]°C	[redacted] months	

*1: The drug substance was produced by the proposed commercial process. *2: The stability testing was ongoing for up to [redacted] months.

The long-term testing showed no significant changes in quality attributes throughout the test period.

The accelerated testing and stress testing showed a tendency toward an increase in [redacted] on SEC.

Based on the above, a shelf-life of [redacted] months was proposed for the drug substance when stored in a [redacted] container, [redacted], and at [redacted] to [redacted]°C.

2.2 Drug product

2.2.1 Description and composition of drug product and formulation development

The drug product is a solution for injection containing 100 or 400 mg of daratumumab in a glass vial (5 or 20 mL). It contains glacial acetic acid, sodium acetate hydrate, sodium chloride, D-mannitol, polysorbate 20, and water for injection as excipients.

2.2.2 Manufacturing process

The manufacturing process of the drug product consists of thawing of the drug substance, pooling and blending, [redacted] filtration, sterile filtration, filling, storage, secondary packaging, testing, and storage. [redacted], [redacted], and [redacted] are defined as critical process steps.

Process validation for the manufacturing process for the drug product has been performed on a commercial scale.

2.2.3 Manufacturing Process Development

The following are major changes made to the drug product manufacturing process during development (Process A, Process B, and the proposed commercial process).

- Process A to Process B: change of [redacted] for [redacted]
- Process B to proposed commercial process: addition of [redacted], and [redacted]

The drug product for phase I/II studies manufactured by Process [redacted] and by Process [redacted] for phase III studies was used in the respective clinical studies [see Section 6.1.2]. For all process changes, comparability of quality attributes was evaluated, and the comparability of drug products between pre-change and post-change has been demonstrated.

A QbD approach has been applied to develop the manufacturing process [see Section 2.3].

2.2.4 Control of drug product

The proposed specification for the drug product consists of content, description, identification (dot-blot), osmolality, pH, purity (opacity, cSDS [reducing and non-reducing], SEC), charge inhomogeneity (cIEF), bacterial endotoxins, extractable volume, foreign insoluble matter, translucent substance, insoluble particulate matters, sterility, [redacted] content, biological activities (ADCC and CDC activities), and assay (ultraviolet-visible absorption spectrophotometry).

2.2.5 Stability of drug product

Main stability studies of the drug product are shown in Table 4.

Table 4. Outline of main stability studies of the drug product

	Drug product specification	No. of batches*1	Storage condition	Study period	Storage package
Long-term testing	100 mg	6	5 ± 3°C	24 months*2	glass vial with [redacted] rubber stopper
	400 mg	3			
Accelerated testing	100 mg	6	[redacted]°C/[redacted]%RH	[redacted] months	
	400 mg	3			
Stress testing	100 mg	6	[redacted]°C/[redacted]%RH	[redacted] months	
	400 mg	3			
Photostability testing	100 mg	1	Overall illumination of ≥1.2 million lux·h and an integrated near ultraviolet energy of ≥200 W·h/m^2		

*1: The drug substance and the drug product were produced by the proposed commercial process. *2: The stability testing was ongoing for up to [redacted] months.

The long-term testing showed no significant changes in quality attributes for both drug products within the range of the parameters tested throughout the test period.

The accelerated testing showed reduction in the [redacted] of [redacted] and [redacted] in [redacted], decrease in the [redacted] in [redacted], a tendency toward increase in [redacted] and [redacted] in SEC, change in the [redacted], a tendency toward increase in [redacted] and [redacted], and decreases in biological activities (ADCC and CDC activities) for both drug products.

The stress testing showed an increase in [redacted], a decrease in [redacted], in addition to the above changes observed in the accelerated testing, for both drug products.

The photostability test showed instability of daratumumab to light.

Based on the above, a shelf-life of 24 months was proposed for the 100 mg and 400 mg drug products when stored in a glass vial with [redacted] rubber stopper, protected from light in a carton, at 2°C to 8°C.

2.3 QbD

A QbD approach was used in the development of the drug substance and drug product, and the quality control strategy was established through identification of CQAs as shown in Table 5.

Table 5. List of CQAs of daratumumab

CQAs of drug substance	[redacted], adventitious virus[redacted], [redacted], mycoplasma[*2]
CQAs common between drug substance and drug product	[redacted], pH, osmolality, [redacted], content, [redacted], [redacted] activity, [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], [redacted], bacterial endotoxins, microorganism contamination, identity (test for identification)
CQAs of drug product	[redacted], [redacted], insoluble particulate matters, [redacted], [redacted]

[redacted]

2.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the quality of the drug substance is adequately controlled. Since the stability test results for the drug product are currently being reviewed, the final decision on the quality of the drug product will be provided in the Review Report (2).

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

3.1 Primary pharmacodynamics

3.1.1 Binding characteristics of daratumumab to CD38 (CTD 4.2.1.1.1, 4.2.1.1.2, 4.2.1.1.12, 4.2.1.1.15)

Binding of daratumumab to human recombinant CD38 protein was investigated in a pharmacokinetic analysis using surface plasmon resonance (SPR) method. The results showed that a dissociation constant (K_D) of 4.36 ± 1.47 nmol/L (arithmetic mean ± standard deviation, n = 3).

The binding of daratumumab to His-labeled human recombinant CD38 protein was assessed by ELISA. The results showed that a 50% effective concentration (EC_{50}) of daratumumab was 55.2 ± 1.09 ng/mL (arithmetic mean ± standard error, n = 3).

The binding of daratumumab to Daudi cell line derived from human Burkitt's lymphoma and CHO-CD38 cell line[1)] was assessed by flow cytometry. The results showed that the EC_{50} of daratumumab was 0.26 ± 1.29 μg/mL for Daudi cell line and 0.47 ± 1.37 μg/mL for CHO-CD38 cell line (arithmetic mean ± standard error).

The binding of daratumumab to UM9, L363, RPMI8226, UM6, XG1, U266, and UM3 cell lines derived from human MM and to the primary cells from 7 patients with MM was assessed by flow cytometry. The results of EC_{50} values of daratumumab binding to each cell line are as shown in Table 6.

Table 6. Binding characteristics of daratumumab to MM-derived cell lines and MM patient-derived primary cells

Cell lines			Primary cells from MM patients		
	n	EC_{50} (μg/mL)		n	EC_{50} (μg/mL)
UM9	2	>10, 0.32	Patient 1	1	0.76
L363	2	>10, 0.15	Patient 2	1	0.84
RPMI8226	5	0.43±0.13	Patient 3	2	0.04, 0.05
UM6	1	NA	Patient 4	1	0.86
XG1	1	0.16	Patient 5	1	0.2
U266	4	NA	Patient 6	1	0.73
UM3	1	0.19	Patient 7	1	0.37

Arithmetic mean ± standard error; individual values are shown when n = 1 or 2; NA, not calculable.

The epitope of daratumumab was assessed by ELISA. The results suggested that the C-terminal region of CD38 protein (amino acids 202, 272, and 274) was important in binding to daratumumab.

The binding of daratumumab to CD38 protein of pig, rabbit, rat, mouse, cynomolgus monkey, and rhesus monkey was assessed by immunohistochemistry (IHC) method. Binding of daratumumab to CD38 did not occur in any of the animal species studied.

The binding of daratumumab to recombinant chimpanzee CD38 protein was assessed in an analysis of kinetics using SPR method. The results showed that the K_D of daratumumab was 4.46 ± 1.66 nmol/L (arithmetic mean ± standard deviation, n = 4). In addition, the binding of daratumumab to Pan EBV3 cell line derived from chimpanzee B cells was assessed by flow cytometry. The results showed that daratumumab bound to Pan EBV3 cells.

[1)] CHO cell line transfected with human CD38 gene.

3.1.2 CDC activity (CTD 4.2.1.1.3)

The CDC activity of daratumumab against MM patients-derived primary cells, Daudi-luc cell line[2)], and CHO-CD38 cell line was investigated in the presence of human plasma using propidium iodide uptake as an indicator. According to the results, the maximum CDC activity[3)] of daratumumab was 56.92% ± 27.87% against MM patients-derived primary cells (arithmetic mean ± standard deviation, n = 13). The maximum CDC activity of daratumumab against each cell line is shown in Table 7.

Table 7. Maximum CDC activity of daratumumab against each cell line

Cell lines	n	Maximum CDC activity (%)
Daudi-luc	6	60 ± 8
CHO-CD38	2	89, 67

Arithmetic mean ± standard deviation; individual values are shown when n = 2.

3.1.3 ADCC activity (CTD 4.2.1.1.4)

The ADCC activity of daratumumab against MM patient-derived primary cells and human-MM JK6L and AMO-1 cell lines was investigated using human peripheral blood mononuclear cells (PBMCs) as effector cells by the chromium release assay. The results showed that the geometric mean of maximum ADCC activity[4)] of daratumumab against MM patient-derived primary cells was 16.1 (95% confidence interval [CI], 6.3, 32.3, n = 4). The maximum ADCC activity of daratumumab against each cell cline is shown in Table 8.

Table 8. Maximum ADCC activity of daratumumab against each cell line

Cell lines	n	Maximum ADCC activity (%)
JK6L	3	48.9 ± 3.27
AMO-1	1	36.3

Arithmetic mean ± standard error; individual value is shown when n = 1.

3.1.4 ADCP activity (CTD 4.2.1.1.5)

The ADCP activity of daratumumab 1 μg/mL against MM patient-derived primary cells from 12 patients was investigated using human mononuclear cell-derived macrophages as measured by phagocytosis rate[5)] and elimination rate[6)] of MM patient-derived primary cells. The results of phagocytosis and elimination rates from the study are shown in Table 9.

2) Daudi cell line transfected with luciferase gene.
3) Percentage of cells with CDC activity.
4) Percentage of cells with ADCC activity.
5) Percentage of macrophages (CD11b-positive cells) phagocytizing the calcein-stained primary cells from MM patients.
6) 100 − (CD11b-negative cells in the presence of daratumumab/CD11b-negative cells in the absence of daratumumab × 100).

Table 9. Daratumumab-induced phagocytosis rate and elimination rate for MM patient-derived primary cells*

	Phagocytosis rate (%)	Elimination rate (%)
Patient 1	9.7 ± 2.9	−17.9 ± 8.3
Patient 2	72.7 ± 4.7	97.4 ± 6.5
Patient 3	45.7 ± 5.3	70.1 ± 33.8
Patient 4	57.1 ± 1.4	66.1 ± 4.4
Patient 5	38.2 ± 4.8	98.7 ± 13.8
Patient 6	50.4 ± 0.6	64.9 ± 2.9
Patient 7	51.9 ± 3.7	90.3 ± 11.1
Patient 8	116.2 ± 8.2	216.5 ± 34.1
Patient 9	51.0 ± 6.6	183.4 ± 18.3
Patient 10	68.9 ± 1.2	114.6 ± 7.4
Patient 11	68.0 ± 4.5	190.9 ± 12.6
Patient 12	69.0±0.4	84.2 ± 7.1

Arithmetic mean ± standard error; n = 3; * these values were calculated, respectively, using the daratumumab-induced phagocytosis rate and elimination rate for Daudi-luc cell line as 100%.

3.1.5 Effect on enzyme activity (CTD 4.2.1.1.6)

The effects of daratumumab on adenosine diphosphate (ADP)-ribosyl cyclase activity of recombinant human CD38 protein and CHO-CD38 cell line were investigated by measuring cyclic guanosine diphosphate ribose (cGDPR) levels. The results showed that a 50% inhibitory concentration (IC_{50}) of daratumumab was 0.86 ± 0.22 μg/mL and 1.21 ± 0.55 μg/mL, respectively (arithmetic mean ± standard error, n = 3).

The effects of daratumumab on cyclic adenosine diphosphate ribose (cADPR) hydrolase activity of recombinant human CD38 protein were investigated by measuring ADPR levels. The results showed that daratumumab activated cADPR hydrolase.

3.1.6 Apoptosis-inducing activity

3.1.6.1 *In vitro* (CTD 4.2.1.1.7, 4.2.1.1.8)

The apoptosis-inducing activity of daratumumab 1 μg/mL in the presence of anti-human Fcγ antibody was assessed in human Burkitt's lymphoma-derived Ramos cell line and human MM-derived OPM-1 cell line and Daudi-luc cell line by measuring annexin V and propidium iodide double staining and activated form of caspase-3 staining. The percentage of apoptotic cells in each cell line is shown in Table 10.

Table 10. Percentage of apoptotic cells in cell lines*

Cell lines	Positive cells for annexin V and propidium iodide (%)	Positive cells for activated form of caspase-3 (%)
Ramos	43.3 ± 5.5	36.7 ± 11.5
OPM-1	14.7 ± 4.8	17.4 ± 8.4
Daudi-luc	21.7 ± 3.8	16.3 ± 7.7

Arithmetic mean ± standard deviation; n = 3; * (percentage of apoptotic cells in the daratumumab group) − (percentage of apoptotic cells in the no-treatment group)

The apoptosis-inducing activity of daratumumab in the presence of anti-human Fcγ antibody was assessed in L363-CD38 cell line[7)] and UM9-CD38 cell line[8)] by annexin V, carbocyanine dye, and 7-AAD staining. The results showed that daratumumab induced apoptosis in these cell lines.

The apoptosis-inducing activity of daratumumab under cocultivation with ⅡA1.6-hFcγRI cells derived from mouse B-cell lymphoma forced to express human Fcγ receptor I was assessed in L363-CD38 cell line and UM9-CD38 cell line by annexin V, carbocyanine dye, and 7-AAD staining. The results showed that daratumumab induced apoptosis in these cell lines.

3.1.6.2 *In vivo* (CTD 4.2.1.1.8)

EL4-CD38 cells[9)] were intra-abdominally inoculated in mice lacking the Fc receptor γ chain[10)]. Using such mice, the apoptosis-inducing activity of DARA-K322A[11)] associated with cross-link formation of Fcγ receptors was assessed by annexin V and 7-AAD staining. The results showed that DARA-K322A induced apoptosis.

3.1.7 Anti-tumor activity of daratumumab against malignant tumor-derived cell lines (CTD 4.2.1.1.5, 4.2.1.1.9, 4.2.1.1.10)

The effects of DARA-K322A and DARA-IgG2-K322A[12)] 250 μg on tumor progression-free survival were investigated by measuring tumor volume in severe combined immunodeficient (SCID)-beige mice subcutaneously transplanted with Daudi-luc cell line (8 mice per group). The results showed that the tumor progression-free survival was statistically significantly longer in the DARA-K322A group than the DARA-IgG2-K322A group ($P < 0.004$, Mantel-Cox log-rank test).

The effects of DARA-K322A and DARA-IgG2-K322A 10 μg on tumor progression-free survival were investigated by measuring bioluminescence in SCID-beige mice transplanted with Daudi-luc cell line injected intravenously into the tail vein (10 mice per group). The results showed that the tumor progression-free survival was statistically significantly longer in the DARA-K322A group than the DARA-IgG2-K322A group ($P < 0.001$, Mantel-Cox log-rank test).

The anti-tumor activity of daratumumab was investigated by measuring bioluminescence in SCID mice transplanted with Daudi-luc cell line injected intravenously into the tail vein. The results are described below.

- The study started on the day of transplantation (Day 0). On Day 0, the mice were given intraperitoneal doses of daratumumab at 0.01, 0.1, 1 or 10 μg. On Day 28, tumor volume (bioluminescence) was calculated. The results showed that a statistically significant increase in

[7)] Human MM-derived L363 cell line transfected with human *CD38* gene.
[8)] Human MM-derived UM9 cell line transfected with human *CD38* gene.
[9)] mouse T-cell lymphoma-derived EL4 cell line transfected with human *CD38* gene.
[10)] Leukocytes of Fc receptor γ chain-deficient mice have no ADCC or ADCP activity.
[11)] Daratumumab that is lacking CDC activity.
[12)] Daratumumab that is lacking CDC and ADCP activities.

anti-tumor activity was observed in all daratumumab groups compared with the control (human anti- keyhole limpet hemocyanin [KLH] antibody) group ($P < 0.001$, two-way analysis of variance).

- The study started on the day of transplantation (Day 0). On Day 7, the mice were given intraperitoneal dose of daratumumab 300 μg. On Days 28 and 34, tumor volume (bioluminescence) was calculated. The results showed that a statistically significant increase in anti-tumor activity was observed in the daratumumab group compared with the control (human anti-KLH antibody) group ($P < 0.001$, one-way analysis of variance).
- The study started on the day of transplantation (Day 0). On Day 14, the mice were given intraperitoneal dose of daratumumab 10 μg. On Day 49, tumor volume (bioluminescence) was calculated. The results showed that a statistically significant increase in anti-tumor activity was observed in the daratumumab group compared with the control (human anti-KLH antibody) group ($P < 0.05$, two-way analysis of variance).

3.2 Secondary pharmacodynamics (CTD 4.2.1.2.1, 4.2.1.2.4, 4.2.1.2.5, and 4.2.1.2.7)

The effects of daratumumab on factors including the release of cytokines were investigated as follows:

- The effects of daratumumab 1.1 to 30 μg/mL on human PBMCs were examined by measuring ^{3}H-labeled thymidine uptake. The results showed that daratumumab did not induce cell proliferation.
- The effects of daratumumab 0.1 to 100 μg/mL on the production of IL-6, IL-1β, and TNF-α were examined by ELISA using human whole blood and PBMCs. According to the results, the production of IL-6 and TNF-α mediated by the Fc of daratumumab was observed when daratumumab was immobilized on a plate.
- The binding of daratumumab 0.05 to 100 μg/mL to platelets was examined by flow cytometry using human whole blood. According to the results, the EC_{50} value for daratumumab could not be calculated.
- Daratumumab did not induce lysis of red blood cells in the presence of human serum.

3.3 Safety pharmacology

In a 6-week intravenous repeated-dose toxicity study, chimpanzees were given daratumumab 5 and 25 mg/kg to investigate the effects of daratumumab on electrocardiograms, body temperature, blood pressure, and general condition. No daratumumab treatment-related effects were observed [see Section 5.2.1].

3.4 Pharmacodynamic drug interactions (CTD 4.2.1.4.1, 4.2.1.4.2)

The ADCC activity of daratumumab against MM patient-derived primary cells and UM9 cell line was investigated using human PBMCs as effector cells by the chromium release assay. The results indicated that the ADCC activity of daratumumab in combination with lenalidomide was higher than that of daratumumab alone.

The ADCC activity of daratumumab, lenalidomide, and bortezomib (BTZ) was investigated using MM patient-derived monocyte by flow cytometry. In each of the following combinations, a higher ADCC

activity was observed in 1) the combination of daratumumab and lenalidomide than in lenalidomide alone, 2) the combination of daratumumab and BTZ than in BTZ alone, and 3) the combination of daratumumab, lenalidomide, and BTZ than in the combination of lenalidomide and BTZ.

The ADCC activity was investigated using MM patient-derived monocyte by flow cytometry for the following combinations, i.e. 1) 4-drug combination of lenalidomide, BTZ, dexamethasone (DEX), and daratumumab and 2) 4-drug combination of BTZ, melphalan, prednisone, and daratumumab. In both combinations, daratumumab enhanced the ADCC activity.

3.R Outline of the review conducted by PMDA

Based on the submitted data and its following review, PMDA concluded that daratumumab is expected to be effective in patients with MM.

3.R.1 Mechanism of action of daratumumab and its efficacy in MM

The applicant's explanation on the mechanism of action of daratumumab and its efficacy in MM patients:

Daratumumab is considered to bind to the CD38 and inhibit tumor proliferation through induction of CDC, ADCC, and ADCP activities in MM cells [see Sections 3.1.2, 3.1.3, and 3.1.4]. Since daratumumab was shown to induce apoptosis in human MM-derived cell lines via Fc receptor-mediated cross-link formation [see Section 3.1.6], such action may contribute to the anti-tumor activity.

In light of the mechanism of action of daratumumab described above, and in consideration of increased CD38 expression in patients with MM (*Am J Clin Pathol.* 2004;121:482-8), daratumumab is expected to be effective in patients with MM.

PMDA accepted the applicant's explanation.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

Because daratumumab binds to human and chimpanzee CD38 [see Section 3.1.1], the pharmacokinetics (PK) of daratumumab in animals was studied in chimpanzees.

4.1 Analytical methods

4.1.1 Measurement of daratumumab

ELISA methods were used to quantify daratumumab in chimpanzee serum using the extracellular domain of immobilized human CD38 and horseradish peroxidase (HRP)-labeled goat anti-human IgG $F(ab')_2$ domain antibody.

4.1.2 Measurement of anti-daratumumab antibodies

ELISA methods were used to quantify anti-daratumumab antibodies in chimpanzee serum using the $F(ab')_2$ domain of immobilized daratumumab and HRP-labeled mouse anti-human IgG Fc domain antibodies.

4.2 Absorption

4.2.1 Repeated-dose studies

Following repeated intravenous administration of daratumumab 5 or 25 mg/kg once every week for 6 weeks to male and female chimpanzees, the serum concentration of daratumumab was assessed (Table 11). Accumulation of daratumumab was noted as a result of repeated administration. Increases in daratumumab exposure (C_{max} and AUC), a decrease in CL, and prolongation of $t_{1/2}$ were observed in a dose proportional manner over the dose range studied. The findings may have occurred because the target-mediated clearance of daratumumab became saturated. Since only one male and female animal received each dose of daratumumab, the applicant explained that a definitive conclusion could not be drawn for the sex differences in the PK of daratumumab.

No anti-daratumumab antibody was detected in either of the animals.

Table 11. PK parameters of daratumumab (male and female chimpanzees, 6-week intravenous repeated dose)

No. of doses	Dose (mg/kg)	Sex	C_{max} (μg/mL)	AUC_t (μg·h/mL)	AUC_{inf} (μg·h/mL)	$t_{1/2}$ (h)	V_z (mL/kg)	CL (mL/h/kg)
1	5	M	100	2,185*1	2,246	38	122.7	2.23
		F	86	2,799*1	2,966	36	86.7	1.69
	25	M	612	25,885*2	40,463	103	91.4	0.62
		F	778	39,158*2	74,458	135	65.6	0.34
3	5	M	129	11,309*1	15,836	88	43.8	0.34
	25	M	630	39,995*1	96,676	231	240.0	0.72
		F	599	62,112*1	215,145	335	164.7	0.34
6	5	M	129	21,450*3	23,171	132	63.8	0.33
	25	M	695	146,729*3	319,583	596	2,205.3	2.56
		F	967	201,462*3	364,102	461	384.4	0.58

n＝1 (individual value); *1, AUC_{168h}; *2, AUC_{144h}; *3, AUC_{528h}

4.3 Distribution

The applicant explanation:

Given that daratumumab is a humanized antibody of IgG subclass that is considered to be distributed primarily in circulating blood, the applicant explained that for the following reason, the tissue distribution of daratumumab was not studied.

- A tissue cross-reactivity study with human and chimpanzee normal tissues demonstrated that the tissue cross-reactivity of daratumumab in the cytoplasm [see Sections 5.7.1.2 and 5.7.1.1]. However, daratumumab is unlikely to be distributed in the tissues because daratumumab does not reach the cytoplasm *in vivo*.

The applicant explained that daratumumab, a humanized antibody of IgG1 subclass, may be transferred across the placenta to the fetus because antibodies in the maternal circulating blood are transferred to the fetus via FcRn of the chorioallantoic placenta in humans (*Birth Defects Res B Dev Reprod Toxicol.* 2009;86:328-44).

4.4 Metabolism and excretion

The applicant's explanation:

As daratumumab is an antibody drug, it is assumed that daratumumab is eliminated via the proteolytic pathway. Therefore, the applicant explained that for this reason, no studies were performed for the metabolism and excretion of daratumumab in accordance with "Preclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals" (PFSB/ELD Notification No. 0323-1, dated March 23, 2012).

The applicant also explained that it is possible that daratumumab is excreted into breast milk, given that human IgG1 was reported to be excreted into breast milk (*Immunol Lett.* 1989;22:235-8); therefore, it plans to add a precautionary statement in the package insert to the effect that administration of daratumumab to breastfeeding women should be avoided, and that if treatment is unavoidable, breastfeeding should be stopped.

4.R Outline of the review conducted by PMDA

Based on the submitted data, PMDA concluded that the explanations provided by the applicant regarding the absorption, distribution, metabolism, and excretion of daratumumab are acceptable.

5. Toxicity and Outline of the Review Conducted by PMDA

Since daratumumab binds to human and chimpanzee CD38 [see Section 3.1.1], Genmab, the company that discovered daratumumab, conducted toxicity studies in chimpanzees. In addition, a 2-week intravenous repeated-dose toxicity study in cynomolgus monkeys was conducted using HuMab-CD38, a humanized antibody of the IgG1 subclass that binds to human and cynomolgus monkey CD38 and shows a comparable ADCC activity to that of daratumumab. Histopathological examination was performed only in the dead animals in the 6-week intravenous repeated-dose toxicity study in chimpanzees.

5.1 Single-dose toxicity

Based on the results of the 6-week intravenous repeated-dose toxicity study in chimpanzees, acute toxicity was evaluated after the first dose of daratumumab [see Section 5.2.1]. The approximate lethal dose of daratumumab was determined to be 5 mg/kg.

5.2 Repeated-dose toxicity

5.2.1 6-week intravenous repeated-dose toxicity study in chimpanzees

Daratumumab was administered once every week for 6 weeks by continuous intravenous infusion over 30 minutes or 1 hour to chimpanzees (n = 1-2/sex/group) at 5 or 25 mg/kg (vehicle, an aqueous solution containing 25 mmol/L sodium acetate, 60 mmol/L sodium chloride, 140 mmol/L mannitol, and 0.006%

polysorbate 20; pH 5.5). Animals were given a 13- or 15-week recovery period following the 6-week dosing period to assess recovery. Based on the fact that findings, which were concluded to be cytokine release syndrome, were observed in the 5 mg/kg group, an intravenous bolus injection of daratumumab 10 mg was administered 24 hours before the first administration in the 25 mg/kg group.

A female animal in the 5 mg/kg group died 1.5 hours after the first administration. As changes in clinical observations, the female animal presented (increased production of mucosae in the trachea and paranasal sinus; sneezing; pale mucosa; and laboured respiration;) massive excretion of foamy fluid on defecation or from the trachea and nostril; overdistention, oedema, and anthracosis in the lungs; left ventricular hypertrophy; chronic infarction of the right ventricular surface; adhesion of the stomach and intestine; and increases in TNF-α, IL-6, and IFN-γ. The cause of death was concluded to be fluid retention in the lungs due to acute anaphylaxis.

In the surviving animals, the following were observed: increases in production of mucosa in the trachea and nasal discharge, soft stools, appetite impaired, platelet count decreased, increased neutrophil count and percentage, decreased lymphocyte count and percentage, decreased red blood cell count and hemoglobin concentration, decreased IgG and IgM concentrations, increased CRP, prolonged APTT, and decreased mononuclear cells in the peripheral blood, bone marrow, and lymph nodes in the 5 mg/kg or higher dose groups; blunting, sneezing, pale mucosa, decreased activity/depression, and decreased serum potassium and total protein in the 25 mg/kg group. Gastrointestinal disorders including more severe findings (diarrhea and bloody stools) and decreased appetite were observed in the 25 mg/kg group until the end of the recovery period. Symptoms and signs other than gastrointestinal disorders and decreased appetite had resolved or were resolving at the end of the recovery period.

Based on the above results, the no-observed-adverse-effect level (NOAEL) in the study was determined to be <5 mg/kg. The C_{max} and $AUC_{0\text{-}7day}$ (129 μg/mL and 11,629 μg·h/mL, respectively) in the 5 mg/kg group (n = 1) were 0.12 and 0.09 times C_{max} and $AUC_{0\text{-}7day}$ at clinical exposure[13)].

5.2.2 2-week intravenous repeated-dose toxicity study in cynomolgus monkeys (reference data, non-GLP study)

HuMab-CD38 was administered once every week for 2 weeks by continuous intravenous infusion over 30 minutes to cynomolgus monkeys (n = 2/sex/group) at 0, 20, or 100 mg/kg (vehicle, an aqueous solution containing 12.6 mmol/L sodium phosphate and 140 mmol/L sodium chloride; pH 7.4). One male and 1 female monkey in each group were given an 8-week recovery period following the 2-week dosing period to assess recovery.

13) In Study 1002 in Japanese MM patients, daratumumab 16 mg/kg was intravenously administered once every week on Days 1 and 22 to 57, and C_{max} and $AUC_{0\text{-}7day}$ on Day 57 were 1,094 μg/mL and 125,836 μg·h/mL, respectively [see Section 6.2.1.1].

No death occurred. In the ≥20 mg/kg group, the following were observed: decreases in red blood cell count, hemoglobin concentrations, and hematocrit; increase in reticulocyte count; decreases in white blood cell count and lymphocyte count; increase in total bilirubin; decrease in IgM concentration; thymic atrophy; atrophy of the lymphoid follicle or lymphoid depletion in the mandibular and mesenteric lymph nodes, Peyer's patch, and spleen; increase in normoblasts and decrease in lymphocytes in the bone marrow; decrease in or depletion of CD38-positive T-cells in the peripheral blood and lymph nodes; and positive findings with direct Coombs test and suppression of increases in serum anti-KLH-specific IgG and IgM antibodies. In the 100 mg/kg group, decreases in IgA and IgG concentrations, small thymus, decreases in thymus weight, and multifocal myelitis were observed. After the end of the 8-week recovery period, decreases in IgM concentration, thymic atrophy, lymphoid depletion in the mesenteric lymph node, and localized infiltration of inflammatory cells in the spinal cord and sciatic nerve were observed. Findings other than those observed after the recovery period had resolved or were resolving afterward. According to the applicant, inflammatory changes of the spinal cord was unlikely to occur in humans because no staining of the spinal cord was observed in the tissues of cross-reactivity study with human tissues and because no such case was reported from the clinical studies.

Based on the above findings, the NOAEL in this study was determined to be <20 mg/kg.

5.3 Genotoxicity

No genotoxicity study was conducted because daratumumab is an antibody drug and would not interact directly with DNA or other chromosomal components.

5.4 Carcinogenicity

No carcinogenicity study was conducted because daratumumab is an antineoplastic drug intended to treat patients with advanced cancer.

5.5 Reproductive and developmental toxicity

No reproductive and developmental toxicity study was conducted because there is no animal species or animal model relevant for the evaluation of reproductive and developmental toxicity of daratumumab [see Section 3.1.1].

5.6 Local tolerance

No local tolerance study was conducted. However, the effects of daratumumab on the administration site were evaluated in the 6-week intravenous repeated-dose toxicity study in chimpanzees [see Section 5.2.1]. The results showed that no local irritation was induced by daratumumab.

5.7 Other studies

5.7.1 Tissue cross-reactivity study

5.7.1.1 Tissue cross-reactivity study with human tissues

The binding of fluorescein isothiocyanate (FITC)-labeled daratumumab to human tissues was investigated using human normal tissues. The results showed that daratumumab bound to lymphoid cells in lymphoid tissues (spleen, tonsils, lymph nodes, and thymus). The binding of daratumumab was observed also in lymphoid tissues (spleen, tonsils, lymph nodes, and thymus), lymphocytes of the ileal serosa and the parathyroid, capillary vessels of the pituitary gland, vascular endothelial cells and epithelial cells of the uterine tube, interstitial cells of the kidney, testis, and thyroid gland, and cytoplasm of the prostate.

5.7.1.2 Tissue cross-reactivity study with chimpanzee tissues

The binding of FITC-labeled daratumumab to chimpanzee tissues was investigated using chimpanzee normal tissues. The results showed that daratumumab bound to lymphoid cells and macrophages, as well as hematopoietic cells of the spleen, tonsils, lymph nodes, and lamina propria of the intestinal tract. The binding of daratumumab was also observed in cytoplasms of the adrenal gland, bone marrow, brain, uterine tube, gastrointestinal tract, heart, kidney, liver, pancreas, pituitary gland, skin, spinal cord, striated muscle, and testis.

5.7.1.3 Tissue cross-reactivity study with cynomolgus monkey tissues

The binding of FITC-labeled HuMab-CD38 to cynomolgus monkey tissues was investigated using cynomolgus monkey normal tissues. The results showed that HuMab-CD38 bound to the blood vessels, marrow lymphocytes, cerebral and cerebellar white matter, uterine cervix, colon and lamina propria of the ileum, interstitial portion of the uterine tube, glomerulus and interstitium of the kidney, sinusoids of the liver, alveolar cells in the lung, T-cells in the lymph nodes, peripheral nerve myelin, retina, choroid membrane, glassy membrane, spinal cord white matter, spleen T cell zone, stomach, striated muscle, T-cells in the thymus medulla and cortex, and tonsil T-cell zone.

5.R Outline of the review conducted by PMDA

Based on the submitted data and the following review, PMDA concluded that non-clinical toxicity evaluation indicated no problems for the clinical use of daratumumab, except for the use of daratumumab in pregnant women and contraception.

5.R.1 Use of daratumumab in pregnant or possibly pregnant women and contraception

PMDA asked the applicant to explain 1) the use of daratumumab in pregnant or possibly pregnant women and 2) the necessity of contraception in male patients for a certain period after administration of daratumumab.

The applicant's explanation:

1) There is no need to contraindicate daratumumab in pregnant or possibly pregnant women in light of the followings:
   - Since the placental transfer of daratumumab, a human antibody of the IgG1 subclass, is considered to occur after organogenesis in primates, the fetal exposure to daratumumab during

organogenesis is presumed to be negligible as compared with the maternal serum daratumumab level.

- Since the reproductivity of CD38 knockout mice was reported to be normal (*Physiol Rev.* 2008;88:841-86), the exposure to daratumumab is unlikely to cause teratogenicity even if the functions of CD38 were affected by the exposure.
- Effects on the immune system and bones are reported in CD38 knockout mice (*FASEB J.* 2003;17:369-75), and administration of daratumumab may influence the fetal immune system and/or bones. However, in view of the fact that daratumumab is eliminated from blood after birth, it is presumed that the effects of daratumumab gradually disappear after birth.
- No events relevant to reproductive and developmental toxicity have been reported in the Japanese and foreign clinical studies or safety information of the foreign marketing experience.

2) Since no reproductive and developmental toxicity study was conducted, the effects of daratumumab on the male fertility remain unknown. However, there is no need for men to use contraception for the following reasons:
   - In the 2-week intravenous repeated-dose toxicity study of HuMab-CD38 in cynomolgus monkeys, no toxicity finding was observed in male reproductive organs [see Section 5.2.2].
   - The reproductive function of CD38 knockout mice was normal (*Physiol Rev.* 2008;88:841-86).
   - Since daratumumab is a human antibody of the IgG1 subclass, it is considered unlikely that daratumumab transfers into the seminiferous tubule by crossing the blood-testis barrier.
   - Daratumumab may be detected in the sperm of a male patient receiving daratumumab. However, based on the level of absorption in the vagina and placental transfer, the exposure of embryo and fetus to daratumumab is presumed to be negligible, and the risk to the embryo-fetal development is considered to be low.

PMDA's review and discussion on the use of daratumumab in pregnant or possibly pregnant women:
The risk of reproductive and developmental toxicity of daratumumab is unclear so far, because no reproductive and developmental toxicity study was conducted and because the evaluation of the reproductive and developmental toxicity of daratumumab based on the findings observed in the CD38 knockout mice is limited. Thus PMDA concluded that daratumumab should be contraindicated in such patients, considering that the use of daratumumab in pregnant or possibly pregnant women is unacceptable.

The effects of daratumumab on male fertility are unclear because differences in reproductive and developmental toxicity may exist between daratumumab and HuMab-CD38 and because the evaluation of the reproductive and developmental toxicity of daratumumab based on the data available from the 2-week intravenous repeated-dose toxicity study of HuMab-CD38 in cynomolgus monkeys is limited. Thus, PMDA concluded that male patients should use effective contraceptive methods during and for a certain period after daratumumab treatment.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

6.1.1 Analytical methods

6.1.1.1 Measurement of daratumumab

Daratumumab in human serum was quantitated by one of the following methods:

1) ELISA with the extracellular region of immobilized human CD38 and the HRP-labeled mouse anti-human IgG1 Fc region antibodies[14] (lower limit of quantitation, 4 ng/mL).
2) Eelectrochemiluminescence (ECL) with immobilized streptavidin, biotin-labeled mouse anti-daratumumab antibodies, and ruthenium-labeled mouse anti-daratumumab antibodies[15] (lower limit of quantification, 5 ng/mL).

6.1.1.2 Measurement of anti-daratumumab antibodies

Anti-daratumumab antibodies in human serum were detected by ECL (methods 1[16] and 2[17]) with immobilized streptavidin, biotin-labeled daratumumab, and ruthenium-labeled daratumumab (detection sensitivity, 0.625 ng/mL in Method 1 and 0.391 ng/mL in Method 2).

Neutralizing antibodies against daratumumab in human serum were determined by fluorescence detection in Daudi cell line derived from human Burkitt's lymphoma and europium-labeled daratumumab (detection sensitivity, 97.46 ng/mL).

The applicant’s explanation about possible effects of the serum daratumumab on the measurement of anti-daratumumab antibodies:

The upper limit of daratumumab level in samples with no effects on the measurement of anti-daratumumab antibodies was 5 and 500 μg/mL, respectively, for the above methods 1) and 2). In clinical studies where the above methods were used, the respective maximum serum daratumumab level at the time of measurement of anti-daratumumab antibodies was 1,336 and 1,764 μg/mL. The results suggest that serum daratumumab might have affected the measurements of anti-daratumumab antibodies by the methods.

6.1.2 Changes made to the drug substance and drug product manufacturing process during development

Changes were made to the manufacturing processes for the drug substance and the drug product during development [see Sections 2.1.4 and 2.2.3]. The following drug products were used in the clinical studies submitted in this application: the drug product for phase I/II studies in the foreign phase I/II studies (Part 1 and Cohorts A to D in Part 2 of Study GEN503 and Study GEN501) and the foreign phase II study (Part 1 of Study 2002); and the drug product for phase III studies in the Japanese phase I study (Study

[14] Samples in Studies 1002, GEN501, 2002, and GEN503 were measured.
[15] Samples in Studies 1001, 1002, 1005, 3003, 3004, and GEN503 were measured.
[16] Samples in Study GEN501 were measured.
[17] Samples in Studies 1001, 1002, 1005, 2002, 3003, 3004, and GEN503 were measured.

1002), the Japanese phase Ib study (Study 1005), the global phase III study (Study 3003), the foreign phase Ib study (Study 1001), the foreign phase I/II study (Cohort E in Part 2 of Study GEN501), the foreign phase II study (Part 2 of Study 2002), and the foreign phase III study (Study 3004).

For all manufacturing changes in the drug substance and drug product from phase I/II studies to proposed commercial drug product, the comparability of quality attributes was evaluated, and it has been confirmed that the drug substance and drug product are comparable before and after the change [see Sections 2.1.4 and 2.2.3].

6.2 Clinical pharmacology

The PK of daratumumab administered as monotherapy and in combination with 1) Ld, 2) Bd, 3) BTd, 4) BMP, or 5) Pd was investigated in patients with cancer.

6.2.1 Japanese clinical studies

6.2.1.1 Japanese phase I study (CTD 5.3.5.2.3-1, Study 1002 [April 2014 to September 2015])

An open-label, uncontrolled study was conducted to investigate the PK of daratumumab in 9 patients with relapsed or refractory MM (9 patients included in the PK analysis). In Part 1 (Weeks 1-10), daratumumab 8 or 16 mg/kg was intravenously administered as a single dose, followed by a 3-week resting period, and then intravenously administered weekly in Weeks 4 to 9. In Part 2 (Week 11 and subsequent weeks), with a cycle of 28 days, daratumumab was intravenously administered every 2 weeks in Cycles 1 to 4 and every 4 weeks in Cycles 5 and subsequent cycles. Parts 1 and 2 were separated by a 2-week resting period.

The PK parameters of daratumumab in Part 1 are shown in Table 12. After the initial dose, $t_{1/2}$ was prolonged and CL decreased with increases in daratumumab dose. Accumulation occurred after the repeated doses of daratumumab in Part 1, whereas decreases in predose concentrations were observed after a repeated dose of daratumumab in Part 2.

Table 12. PK parameters of daratumumab

Dose (mg/kg)	Day of measurement	n	C_{max} (μg/mL)	t_{max} (h)	$AUC_{0\text{-}7day}$ (μg·h/mL)	AUC_{last} (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V_z (mL/kg)
8	Day 1	4	140 ± 52.1	10.6 ± 1.52	10,156 ± 2,989	12,690 ± 4,900	68.2 ± 14.9	0.678 ± 0.313	64.9 ± 26.1
	Day 57	2	332, 369	5.38, 22.6	28,756, 44,749	—	—	—	—
16	Day 1	5	321 ± 72.7	9.64 ± 0.927	28,897 ± 6,903	53,598 ± 24,038	407 ± 515	0.247 ± 0.141	71.7 ± 18.1
	Day 57	3	1,094 ± 399	6.06 ± 2.31	125,836 ± 37,082	—	—	—	—

Arithmetic mean ± standard deviation (individual values when n = 2).—, not calculated.

6.2.1.2 Japanese phase Ib study (CTD 5.3.5.2.4-1, Study 1005 [August 2015 to ongoing (data cut-off date, June 3, 2016)])

An open-label, uncontrolled study was conducted to investigate the PK of daratumumab in 8 patients with relapsed or refractory MM (8 patients included in the PK analysis). In Cycles 1 to 8 (21-day cycle),

daratumumab 16 mg/kg was intravenously administered in combination with Bd[18] weekly in Cycles 1 to 3 and every 3 weeks in Cycles 4 to 8. In Cycle 9 and subsequent cycles (28-day cycle), daratumumab 16 mg/kg was administered as monotherapy every 4 weeks. Serum daratumumab levels were studied.

Daratumumab level (arithmetic mean ± standard deviation) at the end of initial dose, predose on Cycle 3 Day 1, postdose on Cycle 3 Day 1, predose on Cycle 6 Day 1, and postdose on Cycle 6 Day 1 was 354 ± 61.8, 513 ± 138, 865 ± 168, 536 ± 144, 925 ± 160 μg/mL, respectively.

6.2.2 Global study

6.2.2.1 Global phase III study (CTD 5.3.5.1.1-1, Study 3003 [June 2014 to ongoing (data cutoff date, March 7, 2016)])

An open-label, randomized study was conducted to investigate the efficacy and safety of daratumumab in combination with Ld (daratumumab/Ld) in 569 patients with relapsed or refractory MM (282 patients included in the PK analysis). With a cycle of 28 days, daratumumab 16 mg/kg in combination with Ld[19] was intravenously administered weekly in Cycles 1 and 2, every 2 weeks in Cycles 3 to 6, and every 4 weeks in Cycle 7 and subsequent cycles, and serum daratumumab levels were studied.

Daratumumab level at the end of the initial dose, predose on Cycle 3 Day 1, postdose on Cycle 3 Day 1, and predose on Cycle 12 Day 1 was 329 ± 95.9, 608 ± 232, 972 ± 272, and 255 ± 124 μg/mL, respectively. Daratumumab levels in Japanese (20 patients included in the PK analysis) and non-Japanese patients (262 patients included in the PK analysis) at the end of initial dose, predose on Cycle 3 Day 1, and postdose on Cycle 3 Day 1 were 290 ± 52 and 332 ± 98, 563 ± 166 and 611 ± 237, and 900 ± 202 and 978 ± 277 μg/mL, respectively.

The applicant claimed that the combination of daratumumab and Ld is unlikely to cause pharmacokinetic interactions, in consideration of the following:

- The PK parameters of daratumumab in combination with Ld were generally comparable to those for daratumumab monotherapy in a foreign phase II study (Study 2002) [see Section 6.2.3.2].
- Daratumumab seems unlikely to influence the PK of lenalidomide or DEX because daratumumab, an antibody product, is eliminated by a different route from that for lenalidomide or DEX (*J Pharmacol Exp Ther*. 1996;277:105-12; *Int J Hematol*. 2010;92:118-26).

[18] In a cycle of 21 days, BTZ 1.3 mg/m^2 was administered subcutaneously or intravenously on Days 1, 4, 8, and 11 and DEX 20 mg intravenously or orally on Days 1, 2, 4, 5, 8, 9, 11, and 12. In Cycles 1 to 3, DEX 20 mg was administered as prophylaxis for infusion reactions at administration of daratumumab on Day 15.

[19] In a cycle of 28 days, lenalidomide 25 mg was administered orally once daily on Days 1 to 21 (lenalidomide dose, 25 mg for CrCL >60 mL/min, 10 mg [reduced dose] for CrCL 30 to 60 mL/min), and DEX 40 mg intravenously or orally on Days 1, 8, 15, and 22. DEX may be administered in a divided dose of 20 mg before the administration of daratumumab and on the following day.

6.2.3 Foreign clinical studies

6.2.3.1 Foreign phase I/II study (CTD 5.3.5.2.2-1, 5.3.5.2.2-2, and 5.3.5.2.2-3, Study GEN501 [March 2008 to ongoing (data cutoff-date, [redacted])])

An open-label, uncontrolled study was conducted to investigate the PK of daratumumab in 104 patients with relapsed or refractory MM (100 patients included in the PK analysis). In Part 1, daratumumab 0.005 to 24 mg/kg was intravenously administered as a single dose, followed by a 3-week resting period, and then was administered weekly in Weeks 4 to 9. In Cohorts A, B, and C in Part 2, daratumumab 8 mg/kg was administered weekly in Weeks 1 to 7, every 2 weeks in Weeks 8 to 22, and every 4 weeks in Week 24 and subsequent weeks. In Cohorts D and E in Part 2, daratumumab 16 mg/kg was intravenously administered as a single dose, followed by a 3-week resting period, and then administered weekly in Weeks 4 to 9, every 2 weeks in Weeks 10 to 22, and every 4 weeks in Week 24 and subsequent weeks. Serum daratumumab levels were studied.

The dosing conditions for daratumumab in each cohort in Part 2 are shown in Table 13.

Table 13. Dosing conditions for daratumumab in Part 2

Cohort	Dose (mg/kg)	Drug product	Use of pretreatment*1	Total volume after dilution*2 (mL)	Duration of continuous intravenous administration*2 (minimum hours)
A	8	Drug product for phase I/II studies	Yes	500	4
B	8	Drug product for phase I/II studies	Yes	500	6
C	8	Drug product for phase I/II studies	No	1,000	6
D	16	Drug product for phase I/II studies	No	1,000	6
E	16	Drug product for phase III studies	No	1,000	6

*1, administration of daratumumab 10 mg on the previous day of initial dosing; *2, at the initial dosing.

The PK parameters of daratumumab in Part 1 are shown in Table 14.[20] After the initial dose, the C_{max} of daratumumab increased generally in proportion to the dose, whereas the increase in AUC_{inf} was higher than the dose proportionality. After the repeated doses, the increases in C_{max} and AUC_{inf} were higher than the dose proportionality.

[20] Serum daratumumab levels after administration at 0.005 and 0.05 mg/kg were below the lower limit of quantitation at all measurement points, and thus no PK parameters were calculated for these doses.

Table 14. PK parameters of daratumumab in Part 1

Dose (mg/kg)	Measurement day	n	C_{max} (μg/mL)	AUC_{inf} (μg·h/mL)	AUC_t[*1] (μg·h/mL)	$t_{1/2}$ (h)	CL (mL/h/kg)	V (mL/kg)
0.1	Day 1	6	0.297 ± 0.272	—	6.48[*2]	—	—	—
	Day 57	6	0[*2]	—	—	—	—	—
0.5	Day 1	3	4.76 ± 3.65	313[*2]	119 ± 161	20.0[*2]	1.60[*2]	46.1[*2]
	Day 57	3	6.76 ± 3.76	180 ± 221	254 ± 339	12.7 ± 12.3	6.72 ± 6.18	—
1	Day 1	6	20.3 ± 5.87	977 ± 758[*3]	763 ± 657	28.3 ± 17.9[*3]	1.50 ± 0.960[*3]	44.7 ± 5.70[*3]
	Day 57	6	11.8, 28.7[*4]	200, 2,491[*4]	241, 2,212[*4]	9.14, 62.2[*4]	0.473, 4.16[*4]	40.8[*2]
2	Day 1	3	38.1 ± 7.36	1,927 ± 373	1,936 ± 302	25.6 ± 5.61	1.06 ± 0.203	38.2 ± 1.05
	Day 57	3	39.3[*2]	4,232[*2]	3,597[*2]	72.1[*2]	0.586[*2]	58.4[*2]
4	Day 1	3	83.4 ± 16.0	10,063 ± 6,886	6,354 ± 3,401	91.5 ± 59.9	0.726 ± 0.746	54.3 ± 4.00
	Day 57	3	147, 290[*4]	22,629, 253,669[*4]	16,132, 45,533[*4]	108, 685[*4]	0.099, 0.266[*4]	39.0, 95.8[*4]
8	Day 1	3	154 ± 40.8	27,916 ± 16,156	14,900 ± 5,256	132 ± 68.2	0.404 ± 0.314	56.8 ± 6.26
	Day 57	3	427 ± 177	122,536, 250,688[*4]	57,876, 75,655[*4]	203, 376[*4]	0.189 ± 0.0946	44.9, 62.3[*4]
16	Day 1	3	406 ± 72.5	56,894 ± 22,030	35,613 ± 7,687	110 ± 42.0	0.315 ± 0.134	45.2 ± 5.95
	Day 57	3	904, 1,083[*4]	371,159[*2]	171,653[*2]	215[*2]	0.104[*2]	31.9[*2]
24	Day 1	3	500 ± 80.4	97,176 ± 39,900	47,678 ± 14,397	155 ± 36.5	0.287 ± 0.149	58.9 ± 14.2
	Day 57	3	927, 1,399[*4]	290,544, 1,745,923[*4]	123,056, 248,128[*4]	242, 931[*4]	0.109, 0.216[*4]	73.9, 136[*4]

Arithmetic mean ± standard deviation (individual values when n = 1 or 2). *1, $AUC_{0\text{-}7days}$ for the initial dose, and $AUC_{0\text{-}8days}$ on Day 57. *2, n＝1. *3, n＝5. *4, n＝2. —, not calculated.

The PK parameters of daratumumab after the initial dose in Part 2 are shown in Table 15. The applicant explained that no distinct differences in the PK parameters were observed among Cohorts A, B, C and Cohorts D and E.

Table 15. PK parameters of daratumumab in Part 2

Cohort	Dose (mg/kg)	n	C_{max} (μg/mL)	$AUC_{0\text{-}8h}$ (μg·h/mL)
A	8	16	148 ± 31.0	—
B	8	8	127 ± 27.1	—
C	8	6	109 ± 27.9	—
D	16	20	266 ± 80.4	1,444 ± 452
E	16	22	260 ± 104	1,475 ± 773

Arithmetic mean ± standard deviation. —, not calculated.

The applicant's explanation on the nonlinear PK parameters observed in the Japanese phase I study (Study 1002) and the foreign phase I/II study (Study GEN501):

Daratumumab is considered to be eliminated by the route mediated by the binding to the target antigen and the route independent of the target antigen. Dose escalation of daratumumab caused saturation of the elimination route mediated by the binding to the target antigen, resulting in a decrease in CL and prolongation of $t_{1/2}$, leading to the increase of dose exposure that exceeds its proportionality.

6.2.3.2 Foreign phase II study (CTD 5.3.5.2.1-1, 5.3.5.2.1-2, and 5.3.5.2.1-3, Study 2002 [September 2013 to ongoing (data cutoff date, [redacted])])

An open-label, uncontrolled study was conducted to investigate the PK of daratumumab in 124 patients with relapsed or refractory MM (123 patients included in the PK analysis). In Part 1, with a cycle of 28 days, daratumumab 8 mg/kg was intravenously administered every 4 weeks (Treatment 1) or daratumumab 16 mg/kg was intravenously administered weekly in Cycles 1 and 2, every 2 weeks in

Cycles 3 to 6, and every 4 weeks in Cycle 7 and subsequent cycles (Treatment 2). In Part 2, daratumumab was intravenously administered with the same dosing regimen as Treatment 2. Serum daratumumab levels were studied.

The PK parameters of daratumumab are shown in Table 16. After the initial dose, serum daratumumab levels increased with the increases of daratumumab dose. Accumulation occurred after repeated doses of weekly administered daratumumab.

Table 16. PK parameters of daratumumab (μg/mL)

Measurement points	n	8 mg/kg	n*	16 mg/kg*
after initial dose	15	138 ± 33.0	95	313 ± 107
before fifth dose	16	4.15 ± 7.19	91	365 ± 217
after fifth dose	14	163 ± 50.1	90	713 ± 296
before seventh dose	—	—	78	479 ± 274
after seventh dose	—	—	82	843 ± 369
before ninth dose	10	9.78 ± 10.0	73	573 ± 331
after ninth dose	8	168 ± 54.2	76	915 ± 410

Arithmetic mean ± standard deviation. —, not calculated. *, combined data of Parts 1 and 2.

6.2.3.3 Foreign phase Ib study (CTD 5.3.5.4.2-1, Study 1001 [March 2014 to ongoing (data cutoff date, [redacted])])

An open-label, uncontrolled study was conducted to investigate the PK of daratumumab in 133 patients with MM (128 patients included in the PK analysis). The dosage regimen in the study are described below, and the levels of daratumumab, BTZ, thalidomide, and pomalidomide in serum were studied.

(a) With a cycle of 21 days, daratumumab 16 mg/kg was intravenously administered weekly in Cycles 1 and 2 and every 3 weeks in Cycle 3 and subsequent cycles in combination with BTZ and DEX. BTZ 1.3 mg/m^2 was administered subcutaneously on Days 1, 4, 8, and 11 of Cycles 1 to 4 and on Days 1 and 8 of Cycle 5 and subsequent cycles. DEX 20 mg was administered intravenously or orally on Days 1, 2, 4, 5, 8, 9, 15, and 16 of Cycles 1 and 2, Days 1, 2, 4, 5, 8, 9, 11, and 12 of Cycles 3 and 4, and Days 1, 2, 8, and 9 of Cycle 5 and subsequent cycles.
(b) In addition to the above (a), thalidomide 100 mg was administered orally once daily.
(c) With a cycle of 42 days, daratumumab 16 mg/kg was intravenously administered weekly in Cycle 1 and every 3 weeks in Cycle 2 and subsequent cycles in combination with BTZ, melphalan, and prednisone (prednisone is unapproved in Japan). BTZ 1.3 mg/m^2 was administered subcutaneously on Days 1, 4, 8, 11, 22, 25, 29, and 32 of Cycle 1 and on Days 1, 8, 22, and 29 of Cycle 2 and subsequent cycles. Melphalan 9 mg/m^2 was administered orally on Days 1 to 4 of each cycle. Prednisone 60 mg/m^2 was administered intravenously or orally on Days 1 to 4 of each cycle.
(d) With a cycle of 28 days, daratumumab 16 mg/kg was intravenously administered weekly in Cycles 1 and 2, every 2 weeks in Cycles 3 to 6, and every 4 weeks in Cycle 7 and subsequent cycles in combination with pomalidomide and DEX. Pomalidomide 4 mg was administered orally once daily on Days 1 to 21 of each cycle. DEX 40 mg per week was administered intravenously or orally.

The PK parameters of daratumumab in combination with (a) Bd, (b) BTd, (c) BMP, and (d) Pd are shown in Table 17. The PK parameter data were generally comparable with those observed for daratumumab monotherapy in the foreign phase II study (Study 2002) [see Section 6.2.3.2]. Accordingly, the applicant claimed that the above combinations (a) to (d) are unlikely to influence the PK of daratumumab.

Table 17. PK parameters of daratumumab (μg/mL)

Measurement points	n	Combination (a)	n	Combination (b)	n	Combination (c)	n	Combination (d)
after initial dose	5	312 ± 108	12	344 ± 86.1	11	332 ± 57.1	88	360 ± 113
before fourth dose	5	351 ± 78.7	11	260 ± 94.9	8	319 ± 106	8	267 ± 133
after fourth dose	6	684 ± 169	12	619 ± 141	9	665 ± 123	7	683 ± 163
before fifth dose	—	—	—	—	—	—	79	334 ± 199
after fifth dose	—	—	—	—	—	—	77	762 ± 274
before seventh dose	5	508 ± 198	11	404 ± 133	10	588 ± 161	—	—
after seventh dose	6	903 ± 285	12	761 ± 163	11	936 ± 225	—	—
before ninth dose	—	—	—	—	6	383 ± 179	11	498 ± 235
after ninth dose	—	—	—	—	8	696 ± 213	11	959 ± 313

Arithmetic mean ± standard deviation. (a) Bd. (b) BTd. (c) BMP. (d) Pd.

The applicant's explanation on the effects of daratumumab on the PK of BTZ, thalidomide, pomalidomide, melphalan, and prednisone.

The C_{max} and $AUC_{0\text{-}24h}$ of BTZ after the fourth dose of daratumumab in combination with Bd or BTd were 19.5 ± 18.0 ng/mL (arithmetic mean ± standard deviation) and 102 ± 53.3 ng·h/mL, respectively. The C_{max} and $AUC_{0\text{-}24h}$ of thalidomide after the fourth dose of daratumumab in combination with Bd or BTd were 1,145 ± 355 ng/mL and 11,973 ± 2,744 ng·h/mL, respectively. The C_{max} and $AUC_{0\text{-}24h}$ of pomalidomide after the fifth dose of daratumumab in combination with Pd were 43.4 ± 16.0 ng/mL and 557 ± 197 ng·h/mL, respectively.[21)] The C_{max} and $AUC_{0\text{-}24h}$ of BTZ and thalidomide after repeated doses were 21.5 ng/mL and 98.2 ng·h/mL and 1,170 ng/mL and 11,050 ng·h/mL, respectively (*Clin Pharmacokinet.* 2012;51:823-9; *Clin Pharmacokinet.* 2004;43:311-27), and the C_{max} and $AUC_{0\text{-}24h}$ of pomalidomide after repeated doses are estimated to be 53.4 ng/mL and 535.4 ng·h/mL, respectively.[22)] Based on these findings, daratumumab is unlikely to affect the PK of BTZ, thalidomide, and pomalidomide when used in combination with Bd, BTd, and Pd. In addition, the elimination route of daratumumab, an antibody product, differs from that of melphalan or prednisone (*Br Med J.* 1967;2:205-7; *Clin Pharmacol Ther.* 1979;26:73-80). Therefore, daratumumab is also unlikely to influence the PK of melphalan and prednisone.

21) In 5 of 6 patients, pomalidomide was reduced to 3 mg, and the presented PK parameter data are those observed when pomalidomide was administered at 3 mg.

22) The dose was adjusted based on the C_{max} and $AUC_{0\text{-}24h}$ (71.7 ng/mL and 713.8 ng·h/mL, respectively; *J Clin Pharmacol*. 2015;55:563-72) after repeated doses of pomalidomide 4 mg.

6.2.3.4 Foreign phase III study (CTD 5.3.5.1.2-1, Study 3004 [September 2014 to ongoing (data cutoff date, January 11, 2016)])

An open-label, randomized study was conducted to investigate the efficacy and safety of daratumumab in combination with Bd (daratumumab/Bd) in 498 patients with relapsed or refractory MM (225 patients included in the PK analysis). In Cycles 1 to 8 (21-day cycle), daratumumab 16 mg/kg was intravenously administered weekly in Cycles 1 to 3 and every 3 weeks in Cycles 4 to 8 in combination with Bd.[18)] In Cycle 9 and subsequent cycles (28-day cycle), daratumumab 16 mg/kg was intravenously administered as monotherapy every 4 weeks. Serum daratumumab levels were studied.

Daratumumab levels were 318 ± 98.9 at the end of initial dose, 502 ± 196 at predose on Cycle 3 Day 1, 860 ± 263 at postdose on Cycle 3 Day 1, 444 ± 201 at predose on Cycle 6 Day 1, 811 ± 257 at postdose on Cycle 6 Day 1, 371 ± 172 at predose on Cycle 9 Day 1, and 289 ± 133 μg/mL at predose on Cycle 12 Day 1.

6.2.4 Relationship between exposure and changes in QT/QTc interval

In Parts 1 and 2 of the foreign phase I/II study (Study GEN501), the relationship between ΔQTcF and the serum daratumumab level was examined with a linear mixed effect model. The results showed that, no statistically significant relationship between the serum daratumumab levels and ΔQTcF was observed in Part 1, whereas a significant relationship between the serum daratumumab levels and ΔQTcF was noted in Part 2. It is estimated that QTcF is prolonged by 0.0159 ms with an increase of serum daratumumab level by 1 μg/mL. The applicant claimed that the relationship has no clinical significance and that daratumumab administered at the proposed dosage and administration is unlikely to cause clinically significant QT/QTc prolongation in consideration of the following facts: 1) that the epitope for binding of daratumumab exists in the extracellular region of CD38, and thus daratumumab is unlikely to inhibit the hERG channel and to directly affect the ventricular repolarization; and 2) that there was no patient whose QTcF was >500 ms in association with daratumumab administered in Parts 1 and 2 of Study GEN501.

6.2.5 PPK analysis

A population pharmacokinetic (PKK) analysis was performed based on a nonlinear mixed effect model (software program, *NONMEM* Version 7.2.0) using the PK data (694 subjects, 4,426 measuring time points) for daratumumab in combination with other anticancer drugs obtained from the foreign clinical studies (Studies GEN503, 1001, and 3004) and the global study (Study 3003). The PK of daratumumab was described using a 2-compartment model with linear and Michaelis-Menten nonlinear elimination.

In this analysis, the final model was created by using the PKK model[23)] built on the basis of the daratumumab monotherapy data from clinical studies. The examined covariates for the predicted

[23)] The PPK model was created by a PKK analysis (software program, *NONMEM* Version 7.2.0) which was built on the basis of PK data for daratumumab obtained from the foreign clinical studies (Studies GEN501 and 2002; 232 patients, 2,572

maximal trough concentrations included renal impairment[24], hepatic function disorder[25], age, race, concomitant drugs, region, body weight, sex, albumin, type of myeloma, the number of prior therapies, refractory status, and the Eastern Cooperative Oncology Group (ECOG) performance status (PS). The analysis showed that the effects on the predicted maximal trough concentrations were limited for all the covariates.

Based on the above findings, the applicant explained that the clinical significance of the effects of these covariates on the PK of daratumumab is small.

6.2.6 Relationship between exposure and the efficacy and safety

Based on data from Studies 3003, 3004, and 1001 (data from Study GEN503 are included for evaluation on a relationship with the safety), the relationship between daratumumab exposure and the efficacy and safety was investigated. The daratumumab exposure was estimated by the PKK analysis [see Section 6.2.5].

6.2.6.1 Relationship between exposure and efficacy

The relationship between predicted maximal trough concentrations of daratumumab and progression-free survival (PFS) was investigated by the Cox proportional hazard's model. Among the quartiles of the daratumumab exposure, the lowest-exposure quartile showed a tendency toward improvement in the PFS with increases in daratumumab exposure.

6.2.6.2 Relationship between exposure and safety

The relationship between C_{max} after the initial daratumumab dose and the incidence of infusion reactions was investigated. In addition, the relationship between the maximum C_{max} during the weekly treatment period and the incidence of thrombocytopenia, neutropenia, lymphopenia, anemia, and infections was also investigated. The results showed that the incidence of infections tended to increase with increasing daratumumab exposure, whereas no obvious relationship was observed between daratumumab exposure and the incidence of adverse events other than infections.

6.2.7 Effects of decreased renal or liver function on the PK of daratumumab

No clinical study has been conducted to investigate the PK of daratumumab in patients with renal impairment or hepatic function disorder. The applicant, however, explained that the dose of daratumumab does not need to be adjusted in patients with renal impairment or hepatic function disorder because renal impairment or hepatic function disorder is unlikely to influence the PK of daratumumab in light of the points below.

---

measurement points): 1) body weight, albumin, drug product, and type of myeloma were integrated as covariates for CL; and 2) body weight and sex were integrated as covariates for V1.

[24] Renal function is classified as follows: normal, CrCL of ≥90 mL/min; mildly impaired, CrCL of ≥60 mL/min and <90 mL/min; moderately impaired, ≥30 mL/min and <60 mL/min; and severely impaired, <30 mL/min.

[25] Classification according to the U.S. National Cancer Institute Organ Dysfunction Working Group classification.

- Daratumumab is considered to be eliminated by the route mediated by the binding to the target antigen and the route independent of the target antigen, therefore, renal impairment or hepatic function disorder is unlikely to influence the daratumumab exposures.
- Daratumumab is a high-molecular compound (with a molecular weight of approximately 148,000) and thus is not excreted by the kidney.
- Renal impairment and hepatic function disorder were not selected as significant covariates for PK parameters of daratumumab in the PPK analysis [see Section 6.2.5].

6.2.8 Differences in the PK of daratumumab between Japanese and non-Japanese patients

The applicant explained that no obvious discrepancies in the PK of daratumumab were found between Japanese and non-Japanese patients, considering the points below.

- PK parameters at daratumumab monotherapy obtained from the Part 1 of the Japanese phase I study (Study 1002) were compared with those of Part 1 of the foreign phase I/II study (Study GEN501) [see Sections 6.2.1.1 and 6.2.3.1]. The comparison showed that PK of daratumumab was generally similar between the studies.
- PK parameters for daratumumab in combination with Bd (daratumumab/Bd) obtained from the Japanese phase Ib study (Study 1005) were compared with those of the foreign phase III study (Study 3004) [see Sections 6.2.1.2 and 6.2.3.4]. The comparison showed that PK of daratumumab was generally similar between the studies.
- PK parameters for daratumumab in combination with Ld (daratumumab/Ld) obtained from the global phase III study (Study 3003) were compared between Japanese and non-Japanese patients [see Section 6.2.2.1]. The comparison showed that PK of daratumumab was generally similar between them.

6.R Outline of the review conducted by PMDA

6.R.1 Effects of anti-daratumumab antibodies on the PK of daratumumab

The applicant explained the development of anti-daratumumab antibodies and the effects of anti-daratumumab antibodies on the PK of daratumumab as follows:

The presence of anti-daratumumab antibodies was investigated in the foreign phase Ib study (Study 1001), the foreign phase I/II studies (Studies GEN501 and GEN503), the foreign phase II study (Study 2002), the foreign phase III study (Study 3004), the Japanese phase I study (Study 1002), the Japanese phase Ib study (Study 1005), and the global phase III study (Study 3003). Of 511 patients with samples available after the initial daratumumab dose, 2 patients (1 in Study 1001 and 1 in Study 3003) were tested positive for anti-daratumumab antibodies, and 1 patient (in Study 3003) was tested positive for neutralizing antibodies.

However, the number of patients who were positive for anti-daratumumab antibodies was limited, and it was difficult to draw a definitive conclusion on the effects of anti-daratumumab antibodies on the PK of daratumumab.

PMDA's view:

In addition to the applicant's explanation provided above, the possibility that co-existing daratumumab in the serum affects the measurements of anti-daratumumab antibodies performed by the anti-daratumumab antibody assay in the clinical studies cannot be excluded [see Section 6.1.1.2]. Under such circumstance, the evaluation of the effects of anti-daratumumab antibodies on the PK of daratumumab is limited. Therefore, PMDA concluded that information on the effects of anti-daratumumab antibodies on the PK of daratumumab should be continued to be collected and that new information should be appropriately communicated to healthcare professionals if it becomes available.

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety data of daratumumab, in the form of the results from a Japanese phase I study, a Japanese phase Ib study, a global phase III study, a foreign phase I/II study, a foreign phase II study, and a foreign phase III study as shown in Table 18. The applicant submitted reference data from a foreign phase I/II study and a foreign phase Ib study as shown in Table 18.

Table 18. List of clinical studies for efficacy and safety

Data category	Geographical location	Study identifier	Phase	Study population	No. of subjects enrolled	Dosing regimen	Main endpoints
Evaluation	Japan	1002	I	Patients with relapsed or refractory MM	9	Daratumumab 8 or 16 mg/kg was intravenously administered as a single dose, followed by a 3-week resting period, and then administered weekly in Weeks 4-9 (Part 1). Subsequently, with a cycle of 28 days, daratumumab was intravenously administered every 2 weeks in Cycles 1-4 and every 4 weeks in Cycle 5 and subsequent cycles (Part 2).	Safety PK
		1005	Ib	Patients with relapsed or refractory MM	8	In Cycles 1-8 (21-day cycle), daratumumab 16 mg/kg was intravenously administered in combination with Bd[18] weekly in Cycles 1-3 and every 3 weeks in Cycles 4-8. In Cycles 9 and subsequent cycles (28-day cycle), daratumumab 16 mg/kg was intravenously administered as monotherapy every 4 weeks.	Efficacy Safety PK
	Global	3003	III	Patients with relapsed or refractory MM	569 (a) 286 (b)283	(a) Daratumumab/Ld group: With a cycle of 28 days, daratumumab 16 mg/kg in combination with Ld[19] was intravenously administered weekly in Cycles 1 and 2, every 2 weeks in Cycles 3-6, and every 4 weeks in Cycle 7 and subsequent cycles (b) Ld group: With a cycle of 28 days, Ld[19] was administered.	Efficacy Safety
	Foreign	GEN501	I/II	Patients with relapsed or refractory MM	104 (a) 32 (b) 72	(a) Part 1: Daratumumab 0.005-24 mg/kg was intravenously administered as a single dose, followed by a 3-week resting period, and then was administered weekly in Weeks 4-9. (b) Part 2: Daratumumab 8 mg/kg was intravenously administered weekly in Weeks 1-7, every 2 weeks in Weeks 8-22, and every 4 weeks in Week 24 and subsequent weeks or daratumumab 16 mg/kg was intravenously administered as a single dose, followed by a 3-week resting period, and then administered weekly in Weeks 4-9, every 2 weeks in Weeks 10-22, and every 4 weeks in Week 24 and subsequent weeks.	Efficacy Safety PK
		2002	II	Patients with relapsed or refractory MM	124	With a cycle of 28 days, daratumumab 8 mg/kg was intravenously administered every 4 weeks or daratumumab 16 mg/kg was intravenously administered weekly in Cycles 1 and 2, every 2 weeks in Cycles 3-6, and every 4 weeks in Cycle 7 and subsequent cycles.	Efficacy Safety PK
		3004	III	Patients with relapsed or refractory MM	498 (a) 251 (b)247	(a) Daratumumab/Bd group: In Cycles 1-8 (21-day cycle), daratumumab 16 mg/kg in combination with Bd[18] was intravenously administered weekly for Cycles 1-3 and every 3 weeks for Cycles 4-8. In Cycle 9 and subsequent cycles (28-day cycle), daratumumab was intravenously administered as monotherapy every 4 weeks. (b) Bd group: Bd[18] was administered up to 8 cycles.	Efficacy Safety
Reference	Foreign	GEN503	I/II	Patients with relapsed or refractory MM	45 (a) 13 (b) 32	(a) Phase I part: With a cycle of 28 days, daratumumab 2, 4, 8, or 16 mg/kg in combination with Ld[19] was intravenously administered weekly in Cycles 1 and 2, every 2 weeks in Cycles 3-6, and every 4 weeks in Cycle 7 and subsequent cycles. (b) Phase II part: Daratumumab 16 mg/kg was intravenously administered in the regimen described in the above (a).	Safety PK
		1001	Ib	Patients with MM	133 (a) 6 (b) 12 (c) 12 (d) 103	(a) With a cycle of 21 days, daratumumab 16 mg/kg in combination with Bd was intravenously administered weekly in Cycles 1 and 2 and every 3 weeks in Cycle 3 and subsequent cycles. (b) Thalidomide was added and concomitantly administered in addition to the above (a). (c) With a cycle of 42 days, daratumumab 16 mg/kg in combination with BMP was intravenously administered weekly in Cycle 1 and every 3 weeks in Cycle 2 and subsequent cycles. (d) With a cycle of 28 days, daratumumab 16 mg/kg in combination with Pd was intravenously administered weekly in Cycles 1 and 2, every 2 weeks in Cycles 3-6, and every 4 weeks in Cycle 7 and subsequent cycles.	Safety PK

Each clinical study is summarized below.

Major adverse events other than death reported in individual clinical studies are described in Section "7.3 Adverse events reported in clinical studies," and the clinical study data relevant to PK are presented in Section "6.1 Summary of biopharmaceutic studies and associated analytical methods" and Section "6.2 Clinical pharmacology."

7.1 Evaluation data

7.1.1 Japanese clinical studies

7.1.1.1 Japanese phase I study (CTD 5.3.5.2.3-1, Study 1002 [April 2014 to September 2015])

An open-label, uncontrolled study was conducted at 2 study sites in Japan to investigate the safety and PK of daratumumab in patients with relapsed or refractory MM (target sample size, 6 to 12 subjects).

In Part 1 (Weeks 1 to 10), daratumumab 8 or 16 mg/kg was intravenously administered as a single dose, followed by a 3-week resting period, and then intravenously administered weekly in Weeks 4 to 9. In Part 2 (Week 11 and subsequent weeks), with a cycle of 28 days, daratumumab was intravenously administered every 2 weeks in Cycles 1 to 4 and every 4 weeks in Cycle 5 and subsequent cycles.

All 9 subjects enrolled in the study (4 in the 8 mg/kg group and 5 in the 16 mg/kg group) received daratumumab and were included in the safety analysis set. A total of 6 patients (3 in the 8 mg/kg group and 3 in the 16 mg/kg group) were evaluated for dose limiting toxicity (DLT), excluding 1 patient in the 8 mg/kg group who prematurely discontinued treatment due to disease progression and 1 patient with protocol deviation and 1 patient with noncompliance with study treatment in the 16 mg/kg group.

No DLT was observed during the 5-week DLT evaluation period, i.e., from the initial dose of daratumumab to the start of the fourth dose of daratumumab.

As for safety, no deaths occurred during the daratumumab treatment period or within 30 days after the completion of daratumumab treatment.

7.1.1.2 Japanese phase Ib study (CTD 5.3.5.2.4-1, Study 1005 [August 2015 to ongoing (data cutoff date, Jun 3, 2016)])

An open-label, uncontrolled study was conducted at 5 study sites in Japan to investigate the efficacy, safety, and PK of daratumumab in patients with relapsed or refractory MM (target sample size, 6 to 20 subjects).

In Cycles 1 to 8 (21-day cycle), daratumumab 16 mg/kg in combination with Bd[18)] was intravenously administered weekly in Cycles 1 to 3 and every 3 weeks in Cycles 4 to 8. In Cycle 9 and subsequent cycles (28-day cycle), daratumumab 16 mg/kg was administered as monotherapy every 4 weeks.

All 8 patients enrolled in this study received daratumumab and were included in the efficacy and safety analysis sets.

As for efficacy, the response rate as determined by investigators using the IMWG criteria (sCR, CR, very good partial response [VGPR], or PR) was 100% (8 of 8) of subjects, and sCR, CR, VGPR, and PR was reported in 1, 1, 2, and 4 subjects, respectively.

In Cycle 1, which was the DLT evaluation period, DLT was observed in 2 of 8 patients (with Grade 3 thrombocytopenia, increased AST, and increased GGT; more than 1 event occurred in 1 patient).

As for safety, no deaths occurred during the daratumumab treatment period or within 30 days after the completion of daratumumab treatment.

7.1.2 Global study

7.1.2.1 Global phase III study (CTD 5.3.5.1.1-1, Study 3003 [June 2014 to ongoing (data cutoff date, March 7, 2016)])

An open-label, randomized, comparative study was conducted at 136 study sites in 18 countries or regions, including Japan, to compare the efficacy and safety of daratumumab when combined with Ld (daratumumab/Ld) to those of Ld in patients with relapsed or refractory MM (target sample size, 560 subjects).

With a cycle of 28 days, daratumumab 16 mg/kg in combination with Ld[19)] was intravenously administered weekly in Cycles 1 and 2, every 2 weeks in Cycles 3 to 6, and every 4 weeks in Cycle 7 and subsequent cycles in the daratumumab/Ld group, and Ld was administered in the Ld group. Treatment was continued until disease progression or meeting any of the discontinuation criteria in both the daratumumab/Ld and Ld groups.

A total of 569 subjects enrolled and randomized in the study (286 in the daratumumab/Ld group and 283 in the Ld group) comprised the ITT population and were included in the efficacy analysis set. In the ITT population, 564 patients who received the study drug (283 in the daratumumab/Ld group and 281 in the Ld group) were included in the safety analysis set.

The primary endpoint of this study was PFS centrally determined according to the IMWG criteria (*Leukemia*. 2006;20:1467-73). An interim analysis was planned to be performed after 177 events (60% of the target event number of 295) were observed. The type-I error rate associated with the implementation of an interim analysis was to be adjusted by using the O'Brien-Fleming-type Lan-DeMets alpha spending method.

As for efficacy, the results and Kaplan-Meier curves of PFS centrally determined according to the IMWG criteria at the time of the interim analysis (data cutoff date, March 7, 2016) are shown in Table 19 and Figure 1, respectively. As shown in the table and figure, a significant improvement in PFS was

observed in the daratumumab/Ld group as compared with the Ld group, and therefore the IDMC recommended the early termination of this study.

Table 19. Results of interim analysis for PFS (ITT analysis set, centralized evaluation, data cutoff on March 7, 2016)

	Daratumumab/Ld	Ld
Number of patients	286	283
Number of death or worsening (%)	53 (18.5)	116 (41.0)
Median [95% CI] (months)	NE [NE, NE]	18.4 [13.9, NE]
Hazard ratio*1 [95% CI]	0.37 [0.27, 0.52]	
P value (two-sided) *2	<0.0001	

*1, calculated by using the stratified Cox proportional hazard's model adjusted by stratifying factors (disease stage at screening according to the ISS [1, 2, 3], number of previous therapies [1, 2 or 3, 4 or more], previous treatment with lenalidomide). *2, stratified log-rank test (using stratifying factors similar to those used in the Cox proportional hazard's model), two-sided significance level of 0.00612.

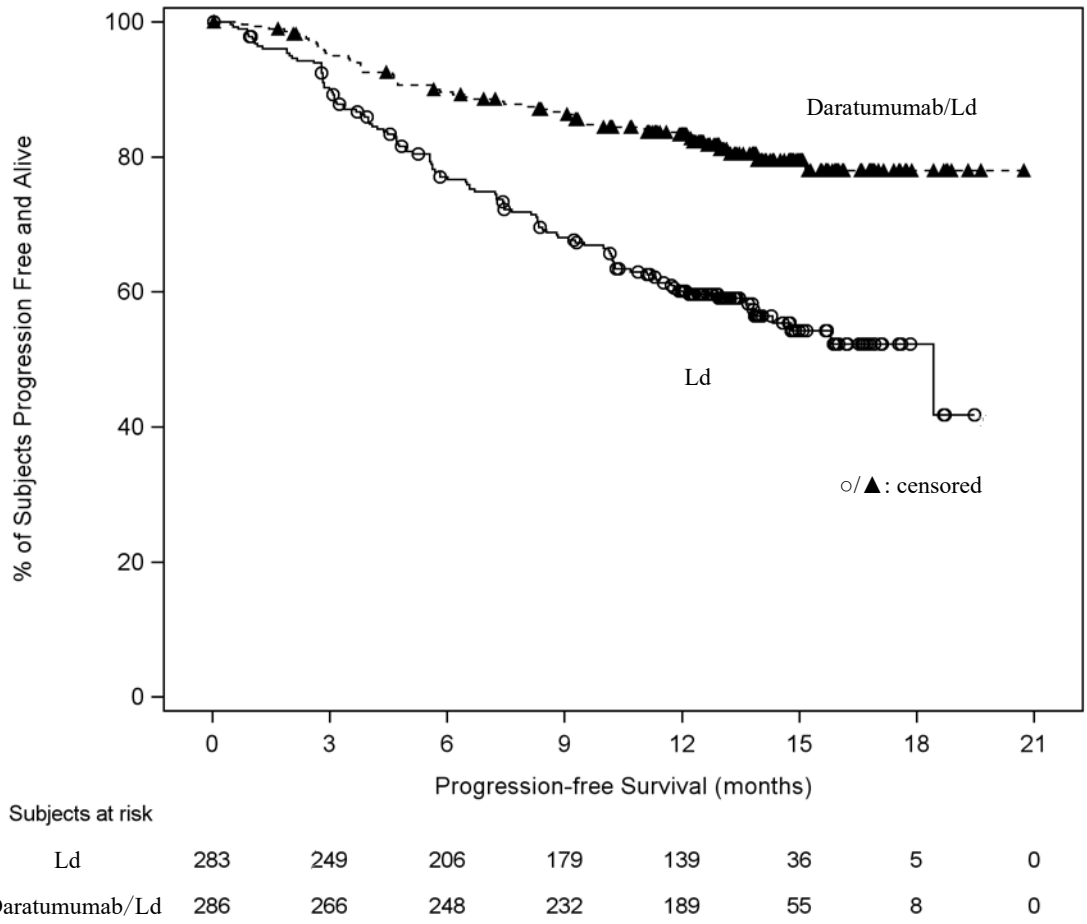


Figure 1. Kaplan-Meier curves at the time of the interim analysis for PFS (ITT analysis set, centralized evaluation, data cutoff on March 7, 2016)

The median of the centrally evaluated PFS in patients with relapsed[26)] MM (189 subjects in the daratumumab/Ld group and 187 subjects in the Ld group) was not estimable (NE) in the daratumumab/Ld group and 18.4 months in the Ld group (hazard ratio [95% CI], 0.29 [0.18, 0.46]). The

[26)] Patients with previous treatment with ≥1 regimen, did not meet the definition of refractory, and had progressive disease.

median of the centrally evaluated PFS in patients with refractory[27)] MM (97 subjects in the daratumumab/Ld group and 96 subjects in the Ld group) was NE in the daratumumab/Ld group and 12.2 months in the Ld group (hazard ratio [95% CI], 0.46 [0.28, 0.77]).

As for safety, deaths during the study treatment period or within 30 days after the completion of treatment occurred in 12 of 283 subjects (4.2%) in the daratumumab/Ld group and 16 of 281 subjects (5.7%) in the Ld group. The causes of death other than disease progression (1 subject in the daratumumab/Ld group and 4 subjects in the Ld group) included the following: septic shock in 3 subjects; pneumonia in 2; acute monocytic leukaemia, pneumonia bacterial, cardiopulmonary failure, multi-organ failure, acute renal failure, and febrile neutropenia in 1 each in the daratumumab/Ld group. Pneumonia, renal failure, septic shock, nervous system disorder, lung adenocarcinoma, cerebral haemorrhage, cardiac arrest, pulmonary oedema, acute respiratory failure, sepsis, and acute renal failure in 1 each in the Ld group. Among these events, a causal relationship to the study drug could not be ruled out for pneumonia in 2 patients, septic shock in 1, acute monocytic leukaemia in 1, pneumonia bacterial in 1, and multi-organ failure in 1 of the daratumumab/Ld group.

7.1.3 Foreign clinical studies

7.1.3.1 Foreign phase I/II study (CTD 5.3.5.2.2-1, 5.3.5.2.2-2, and 5.3.5.2.2-3, Study GEN501 [March 2008 to ongoing (data cutoff-date, [redacted])])

An open-label, uncontrolled study was conducted to investigate the safety of daratumumab in patients with relapsed or refractory MM (target sample size, 26-62 subjects in Part 1, a maximum of 80 subjects in Part 2, a maximum of 112 subjects in total). Parts 1 and 2 were conducted at 4 and 6 study sites outside Japan, respectively.

In Part 1, daratumumab 0.005, 0.05, 0.10, 0.50, 1, 2, 4, 8, 16, or 24 mg/kg was intravenously administered as a single dose, followed by a 3-week resting period, and then was intravenously administered weekly in Weeks 4 to 9. In Part 2, daratumumab 8 mg/kg was intravenously administered weekly in Weeks 1 to 7, every 2 weeks in Weeks 8 to 22, and every 4 weeks in Week 24 and subsequent weeks, or daratumumab 16 mg/kg was intravenously administered as a single dose, followed by a 3-week resting period, and then intravenously administered weekly in Weeks 4 to 9, every 2 weeks in Weeks 10 to 22, and every 4 weeks in Week 24 and subsequent weeks. Treatment was to be continued until Week 96, disease progression, or meeting any of the discontinuation criteria.

Daratumumab was administered to all 32 subjects enrolled in Part 1 of this study (1 each in the 0.005 mg/kg group and the 0.05 mg/kg group, 6 in the 0.10 mg/kg group, 3 in the 0.50 mg/kg group, 6 in the 1 mg/kg group, 3 each in the 2 mg/kg, 4 mg/kg, 8 mg/kg, 16 mg/kg, and 24 mg/kg groups) and all 72 subjects enrolled in Part 2 (30 in the 8 mg/kg group and 42 in the 16 mg/kg group), and all these patients were included in the safety analysis set. All 32 patients enrolled in Part 1 were evaluated for DLT.

27) Patients who had minimal or less response to the previous therapies or had PD during the previous treatment or within 60 days after completion of the previous treatment.

In Part 1 as the DLT evaluation period, DLT was observed in 1 of 6 patients in the 0.10 mg/kg group (Grade 3 anaemia) and 1 of 6 patients in the 1 mg/kg group (Grade 3 hepatic function abnormal), but the MTD was not reached.

As for safety, deaths during the daratumumab treatment period or within 30 days after the completion of daratumumab treatment occurred in no subject in Part 1 and in 3 of 72 subjects (4.2%; 1 in the 8 mg/kg group and 2 in the 16 mg/kg group) in Part 2. The cause of death other than disease progression (1 patient in the 8 mg/kg group and 1 patient in the 16 mg/kg group) was pneumonia in 1 patient in the 16 mg/kg group, and it was concluded to be unrelated to the study drug.

7.1.3.2 Foreign phase II study (CTD 5.3.5.2.1-1, 5.3.5.2.1-2, and 5.3.5.2.1-3, Study 2002 [September 2013 to ongoing (data cutoff date, [redacted])])

An open-label, uncontrolled study was conducted to investigate the efficacy, safety, and PK of daratumumab in patients with relapsed or refractory MM (target sample size, a maximum of 90 and 60 subjects in Parts 1 and 2, respectively) at 26 study sites outside Japan.

In Part 1, with a cycle of 28 days, daratumumab 8 mg/kg was intravenously administered every 4 weeks (Treatment 1) or daratumumab 16 mg/kg was intravenously administered weekly in Cycles 1 and 2, every 2 weeks in Cycles 3 to 6, and every 4 weeks in Cycle 7 and subsequent cycles (Treatment 2). In Part 2, daratumumab was intravenously administered with the same dosing regimen as Treatment 2. Treatment was to be continued until disease progression or meeting any of the discontinuation criteria.

Daratumumab was administered to all 59 subjects enrolled in Part 1 (18 subjects28) in the 8 mg/kg group and 41 subjects in the 16 mg/kg group) and all 65 subjects enrolled in Part 2. All these subjects were enrolled in the efficacy and safety analysis sets.

As for efficacy, the response rate determined by the IRC using the IMWG criteria (sCR, CR, VGPR, or PR) was 11.1% (2 of 18 patients) in the 8 mg/kg group and 29.2% (31 of 106 patients) in the 16 mg/kg group[29)].

As for safety, deaths during the study treatment period or within 30 days after the last dose occurred in none of the subjects in 8 mg/kg group and 12 of 106 subjects (11.3%) in the 16 mg/kg group. Causes of death other than disease progression (10 patients) included general physical health deterioration and cardio-respiratory arrest in 1 patient each, and both were concluded to be unrelated to the study drug.

[28)] The response rate (sCR, CR, VGPR, or PR) did not meet the continuation criteria defined in the study protocol, and therefore treatment with daratumumab 8 mg/kg was discontinued. Among patients in the 8 mg/kg group, 3 patients continued to receive daratumumab in the 16 mg/kg group. These 3 patients were included in the analysis of the daratumumab 8 mg/kg group.

[29)] Pooled data of Parts 1 and 2.

7.1.3.3 Foreign phase III study (CTD 5.3.5.1.2-1, Study 3004 [September 2014 to ongoing (data cutoff date, January 11, 2016)])

An open-label, randomized, comparative study was conducted to compare the efficacy and safety of daratumumab when combined with Bd (daratumumab/Bd) to those of Bd in patients with relapsed or refractory MM (target sample size, 480 subjects) at 117 study sites outside Japan.

In the daratumumab/Bd group, in Cycles 1 to 8 (21-day cycle), daratumumab 16 mg/kg in combination with Bd[18)] was intravenously administered weekly in Cycles 1 to 3 and every 3 weeks in Cycles 4 to 8, and in Cycle 9 and subsequent cycles (28-day cycle), daratumumab 16 mg/kg was intravenously administered as monotherapy every 4 weeks. In the Bd group, Bd was administered up to 8 cycles. In both groups, treatment was to be continued until disease progression or meeting any of the discontinuation criteria.

A total of 498 subjects enrolled and randomized in this study (251 in the daratumumab/Bd group and 247 in the Bd group) comprised the ITT population and were included in the efficacy analysis set. In the ITT population, 480 subjects receiving the study drug (243 in the daratumumab/Bd group and 237 in the Bd group) were included in the safety analysis set.

The primary endpoint of this study was PFS centrally determined according to the IMWG criteria. An interim analysis for evaluation of the efficacy was planned to be performed after 177 events (60% of the target event number of 295) were observed. The significance level associated with the implementation of an interim analysis was to be adjusted by using the O'Brien-Fleming-type Lan-DeMets α spending method.

As for efficacy, the results and Kaplan-Meier curves of PFS centrally determined according to the IMWG criteria at the time of the interim analysis (data cutoff date, January 11, 2016) are shown in Table 20 and Figure 2, respectively. As shown in the table and figure, a significant improvement in PFS was observed in the daratumumab/Bd group as compared with the Bd group, and therefore the IDMC recommended the early termination of this study.

Table 20. Results of the interim analysis for PFS (ITT analysis set, central evaluation, data cutoff on January 11, 2016)

	Daratumumab/Bd	Bd
Number of patients	251	247
Number of death or worsening (%)	67 (26.7)	122 (49.4)
Median [95% CI] (months)	NE [12.3, NE]	7.2 [6.2, 7.9]
Hazard ratio*1 [95% CI]	0.39 [0.28, 0.53]	
P value (two-sided) *2	<0.0001	

*1, calculated by using the stratified Cox proportional hazard's model adjusted by stratifying factors (disease stage at screening according to the ISS [1, 2, 3], the number of previous therapies [1, 2 or 3, ≥4], previous treatment with BTZ).
*2, stratified log-rank test (using stratifying factors similar to those used in the Cox proportional hazard's model), two-sided significance level of 0.0102.

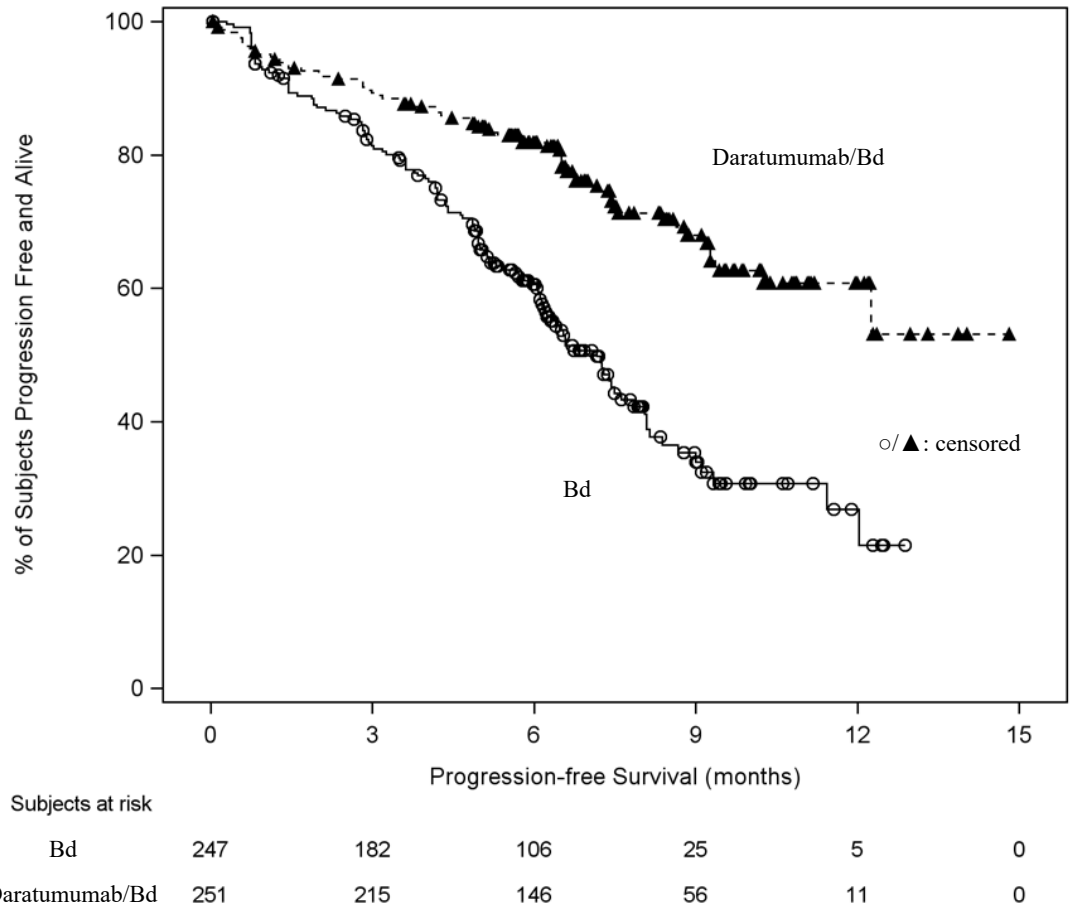


Figure 2. Kaplan-Meier curves at the time of the interim analysis for PFS (ITT analysis set, centralized evaluation, data cutoff on January 11, 2016)

The median of the centrally evaluated PFS in patients with relapsed[26)] MM (147 subjects in the daratumumab/Bd group and 134 subjects in the Bd group) was 12.3 months in the daratumumab/Bd group and 8.1 months in the Bd group (hazard ratio [95% CI], 0.36 [0.22, 0.58]). The median of the centrally evaluated PFS in patients with refractory[27)] MM (104 subjects in the daratumumab/Bd group and 113 subjects in the Bd group) was 9.3 months in the daratumumab/Bd group and 6.1 months in the Bd group (hazard ratio [95% CI], 0.46 [0.30, 0.71]).

As for safety, deaths during the study treatment period or within 30 days after the completion of treatment occurred in 13 of 243 patients (5.3%) in the daratumumab/Bd group and 13 of 237 patients (5.5%) in the Bd group. Causes of death other than disease progression (2 subjects in the daratumumab/Bd group and 3 subjects in the Bd group) included the following: in the daratumumab/Bd group, respiratory failure and ischaemic stroke in 2 patients each, cerebral infarction, organising pneumonia, acute coronary syndrome, cardiogenic shock, duodenal ulcer, general physical health deterioration, and cardiac arrest in 1 patient each; in the Bd group, general physical health deterioration, septic shock, tracheobronchitis, cardiac arrest, pulmonary embolism, condition aggravated, pneumonia, pulmonary oedema, cerebrovascular accident, and myeloma cast nephropathy in 1 patient each. Among

these events, a causal relationship to the study drug could not be ruled out for organising pneumonia, acute coronary syndrome, ischaemic stroke, and duodenal ulcer in 1 patient each in the daratumumab/Bd group and tracheobronchitis in 1 patient in the Bd group.

7.2 Reference data

7.2.1 Foreign clinical studies

7.2.1.1 Foreign phase I/II study (CTD 5.3.5.4.1-1, Study GEN503 [June 2016 to ongoing (data cutoff date, October 2, 2015)])

An open-label, uncontrolled study was conducted to investigate the safety of daratumumab in combination with Ld in patients with relapsed or refractory MM (target sample size, 42 to 58 subjects) at 11 sites outside Japan.

All 45 subjects enrolled in the study (13 in the Phase I part and 32 in the Phase II part) received the study drug and were included in the safety analysis set.

As for safety, deaths during the study treatment period or within 30 days after the treatment occurred in no patient in the Phase I part and in 1 of 32 patients (3.1%) in the Phase II part. The cause of death was pneumonia viral for which a causal relationship to study drug could not be ruled out.

7.2.1.2 Foreign phase Ib study (CTD 5.3.5.4.2-1, Study 1001 [March 2014 to ongoing (data cutoff date, [redacted])])

In MM patients[30] (target sample size, 190 subjects), an open-label, uncontrolled study was conducted to investigate the safety of daratumumab in combination with (a) Bd, (b) BTd, (c) BMP, and (d) Pd[31] at 20 sites outside Japan.

All 133 patients enrolled in this study (6 in [a], 12 in [b], 12 in [c], and 103 in [d]) received the study drug and were included in the safety analysis.

As for safety, deaths during the study drug treatment period or within 30 days after the treatment occurred in no patient for (a), (b), and (c) and in 7 of 103 patients (6.8%) for (d). Causes of death other than disease progression (2 patients) included interstitial lung disease, cerebrovascular accident, progressive multifocal leukoencephalopathy, respiratory failure, and sepsis in 1 patient each. A causal relationship to the study drug could not be ruled out for the event of progressive multifocal leukoencephalopathy in 1 patient.

[30] Previously treated MM patients received Pd as a concomitant drug, and treatment-naïve MM patients received drugs other than Pd.

[31] Patients receiving the combination of carfilzomib + DEX or carfilzomib + lenalidomide + DEX were eligible, but patient enrollment was still ongoing at the time of data cutoff.

7.R Outline of the review conducted by PMDA

7.R.1 Data for review

Among the evaluation data submitted, PMDA regarded the global phase III study (Study 3003) and the foreign phase III study (Study 3004) both conducted in patients with relapsed or refractory MM as the pivotal studies for evaluation of the efficacy and safety of daratumumab and therefore decided to use data mainly from these studies for its review.

PMDA decided to evaluate the efficacy and safety of daratumumab in Japanese patients mainly based on the data from the global phase III study (Study 3003) in patients with relapsed or refractory MM. PMDA decided to review data on the efficacy of daratumumab in Japanese patients in Study 3003 from the view point of consistency between the overall patient population and the Japanese patient population in Study 3003, according to the "Basic Principles on Global Clinical Trials" (PFSB/ELD Notification No. 0928010, dated September 28, 2007) and the "Reference cases for Basic Principles on Global Clinical Trials" (Administrative Notice, dated September 5, 2012).

7.R.2 Efficacy

Based on the review shown below, PMDA concluded that the efficacy of daratumumab is demonstrated in patients with relapsed or refractory MM.

7.R.2.1 Controls

The applicant's justification for selection of control groups in Studies 3003 and 3004:

In 2014 when Studies 3003 and 3004 were started, the National Comprehensive Cancer Network (NCCN) Guidelines (v.2.2014) recommended the treatment with LD[32)] or Bd for patients with relapsed or refractory MM, who were eligible for the 2 studies, based on data from foreign clinical studies (*New Engl J Med*. 2007;357:2123-32; *Br J Haematol*. 2004;127:165-72). In a foreign clinical study in patients with primary MM, a tendency toward improvement in overall survival (OS) and lower incidences of venous thrombotic events and infections were observed in Ld[33)] group as compared with the LD group (*Lancet Oncol*. 2010;11:29-37). In consideration of these, Ld and Bd were selected as active controls for Studies 3003 and 3004.

PMDA accepted the applicant's justification.

7.R.2.2 Efficacy endpoints

The applicant's justification for the use of PFS as the primary efficacy endpoint of Studies 3003 and 3004:

32) With a cycle of 28 days, lenalidomide 25 mg was orally administered once daily on Days 1 to 21, and DEX 40 mg was orally administered once daily on Days 1 to 4, 9 to 12, and 17 to 20 in Cycles 1 to 4 and Days 1 to 4 in Cycle 5 and subsequent cycles.

33) With a cycle of 28 days, lenalidomide 25 mg was orally administered once daily on Days 1 to 21, and DEX 40 mg was orally administered weekly.

MM is an incurable disease that is refractory to currently available therapies and is characterized by multiple relapses. Duration of response is reported to shorten with increasing number of previous therapies in MM patients (*Mayo Clin Proc.* 2004;79:867-74). While treatment for patients with relapsed or refractory MM is intended to prolong their survival, it is expected that prolonged PFS can delay the disease progression and the time to the next-line therapy (*Leukemia.* 2006;20:1467-73). Therefore, PFS was selected as the primary efficacy endpoint for Studies 3003 and 3004.

PMDA's review:

The applicant's justification is generally acceptable, but OS is also important for the evaluation of therapeutic responses in patients with relapsed or refractory MM, for which a standard therapy has not yet been established. Therefore, PMDA decided to review data mainly on PFS which was selected as the primary endpoint and was centrally evaluated according to the IMWG criteria and also to assess data on OS.

7.R.2.3 Results of efficacy evaluation

The superiority of daratumumab in combination with Ld (daratumumab/Ld) to Ld and daratumumab in combination with Bd (daratumumab/Bd) to Bd was confirmed by using the primary efficacy endpoint, PFS centrally determined according to the IMWG criteria in Studies 3003 and 3004 [see Sections 7.1.2.1 and 7.1.3.3]. In a sensitivity analysis, PFS was evaluated by investigators according to the IMWG criteria, and the evaluation results are shown in Table 21.

Table 21. Results of the interim analysis for PFS (ITT analysis set, investigators' assessment, data cutoff on March 7, 2016 for Study 3003 and January 11, 2016 for Study 3004)

	Study 3003		Study 3004	
	Daratumumab/Ld	Ld	Daratumumab/Bd	Bd
Number of patients	286	283	251	247
Number of death or worsening (%)	52 (18.2)	121 (42.8)	73 (29.1)	133 (53.8)
Median [95% CI] (months)	NE [NE, NE]	17.1 [13.6, NE]	12.0 [10.3, NE]	6.6 [6.2, 7.5]
Hazard ratio*1 [95% CI]	0.35 [0.25, 0.49]		0.37 [0.28, 0.51]	
P value (two-sided) *2	<0.0001		<0.0001	

*1, calculated by using the stratified Cox proportional hazard's model adjusted by stratifying factors (disease stage at screening according to the ISS [1, 2, 3], the number of previous therapies [1, 2 or 3, ≥4], previous treatment with lenalidomide [Study 3003] or BTZ [Study 3004]). *2, stratified log-rank test (using stratifying factors similar to those used in the Cox proportional hazard's model).

Results of the interim analysis for OS as the secondary endpoint of Studies 3003 and 3004 (data cutoff date of March 7, 2016, for Study 3003 and January 11, 2016, for Study 3004)[34)] are shown in Table 22 and Figure 3.

[34)] If there was a statistically significant difference in PFS, it had been decided to conduct a test according to the sequential testing procedure prespecified in the protocol to adjust for multiplicity with other secondary endpoints.

Table 22. Results of the interim analysis for OS
(ITT analysis set, data cutoff on March 7, 2016 for Study 3003 and January 11, 2016 for Study 3004)

	Study 3003		Study 3004	
	Daratumumab/Ld	Ld	Daratumumab/Bd	Bd
Number of patients	286	283	251	247
Number of deaths (%)	30 (10.5)	45 (15.9)	29 (11.6)	36 (14.6)
Median [95% CI] (months)	NE [NE, NE]	20.3 [20.3 NE]	NE [NE, NE]	NE [NE, NE]
Hazard ratio*1 [95% CI]	0.64 [0.40, 1.01]		0.77 [0.47, 1.26]	
P value (two-sided) *2	0.0534		0.298	

*1, calculated by using the unstratified Cox proportional hazard's model. *2, unstratified log-rank test, two-sided significance level of 0.0001.

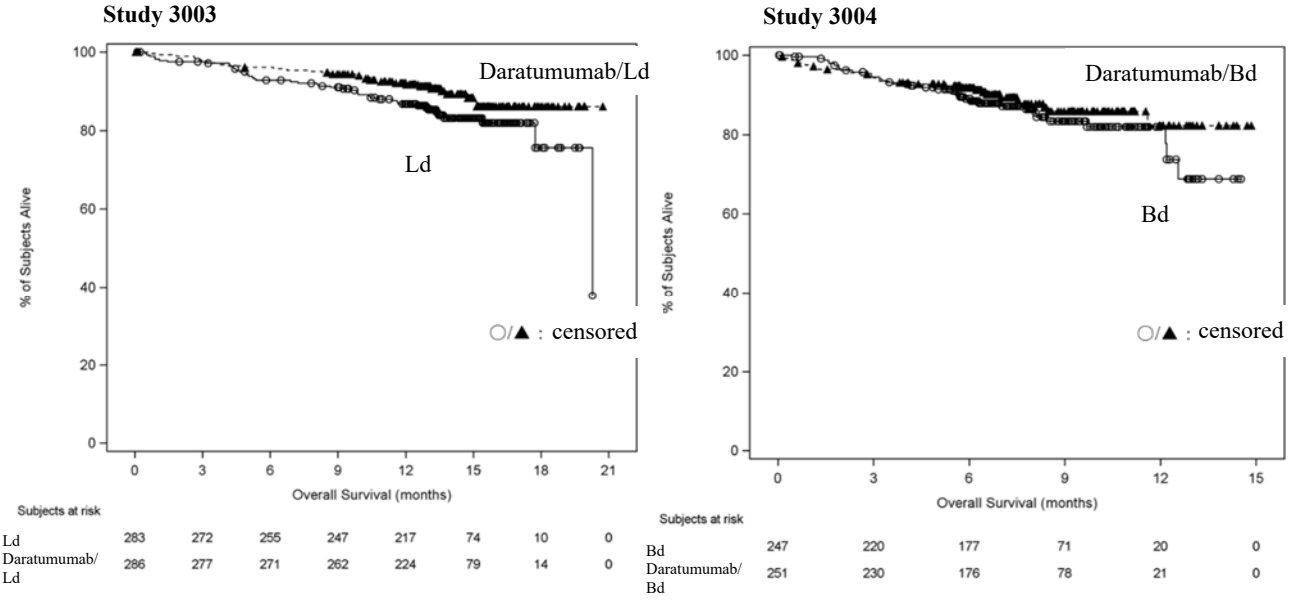


Figure 3. Kaplan-Meier curves at the time of the interim analysis for OS
(ITT analysis set, data cutoff on March 7, 2016 for Study 3003 and January 11, 2016 for Study 3004)

Results and Kaplan-Meier curves of PFS centrally assessed according to the IMWG criteria at the time of the interim analysis in Japanese patients in Study 3003 are shown in Table 23 and Figure 4.

Table 23. Results of the interim analysis for PFS in Japanese patients (ITT analysis set, central evaluation, data cutoff on March 7, 2016)

	Daratumumab/Ld	Ld
Number of patients	21	15
Number of death or worsening (%)	3 (14.3)	6 (40.0)
Median [95% CI] (months)	NE [9.4, NE]	NE [3.8, NE]
Hazard ratio*1 [95% CI]	0.28 [0.07, 1.14]	

*, calculated by using the stratified Cox proportional hazard's model adjusted by stratifying factors (disease stage at screening according to the ISS [1, 2, 3], number of previous therapies [1, 2 or 3, ≥4], previous treatment with lenalidomide).

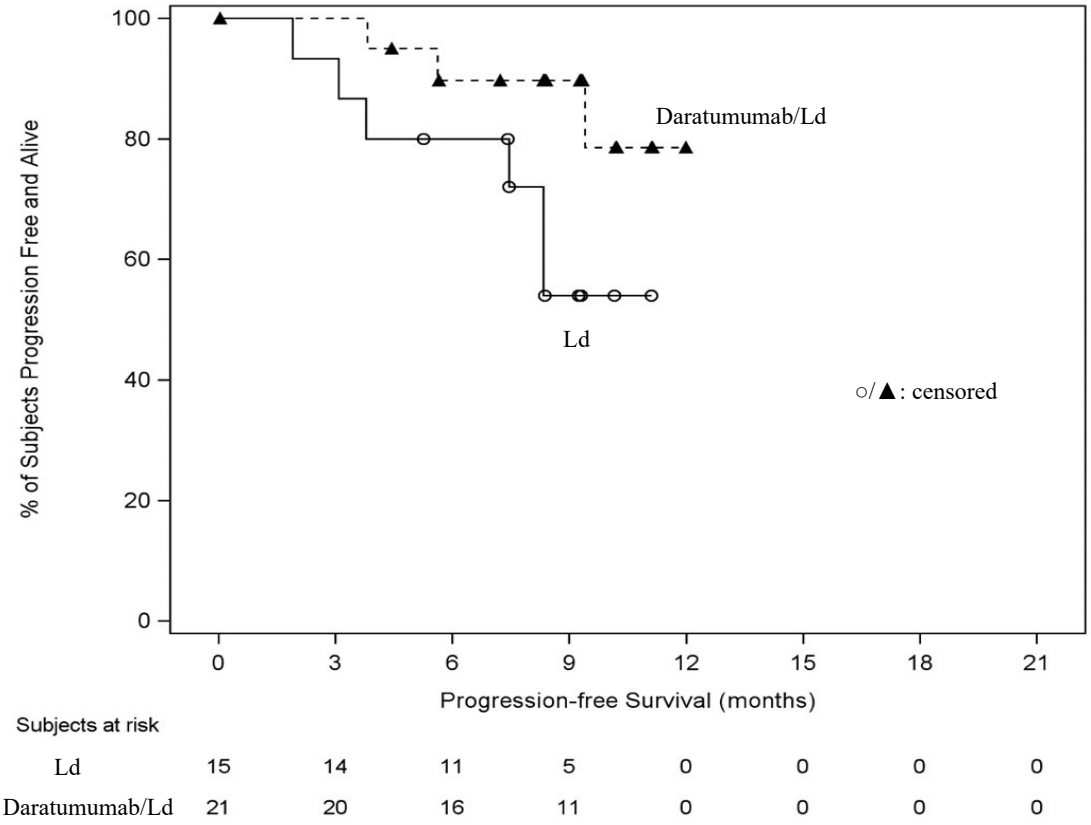


Figure 4. Kaplan-Meier curves at the time of the interim analysis for PFS in Japanese patients (ITT analysis set, central evaluation, data cutoff on March 7, 2016)

In Study 1005, the response rate of daratumumab in combination with Bd (daratumumab/Bd) was 100% (8 of 8 patients) [see Section 7.1.1.2]. In Study 3004, the response rate was 82.9% (199 of 240 patients) in the daratumumab/Bd group and 63.2% (148 of 234 patients) in the Bd groups.

PMDA's review:

In Studies 3003 and 3004, the superiority of daratumumab over the controls were demonstrated in the primary endpoint of centrally evaluated PFS according to the IMWG criteria, and the observed improvement in PFS is considered to be clinically meaningful. Furthermore, there was no obvious tendency toward reduction in OS in the daratumumab groups as compared with the control groups. Although the evaluation was limited because of the small size of Japanese patient population in Studies 3003 and 1005, no clear differences were identified in the PFS results between the Japanese patient population in Studies 3003 and the overall patient population. In addition, a certain number of patients responded to the treatment with daratumumab/Bd in Study 1005.

Based on the above, PMDA concluded that the efficacy of daratumumab has been demonstrated in patients with relapsed or refractory MM.

7.R.3 Safety [for adverse events, see Section "7.3 Adverse events reported in clinical studies"]

Based on the review shown below, PMDA concluded that infusion reaction, bone marrow depression, infections, and haemolysis are adverse events of special interest and that attention should be paid to the occurrence of these adverse events when daratumumab is used.

PMDA concluded that daratumumab is tolerable when appropriate measures (e.g., follow-up and management of adverse events) are taken by a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancies although attention should be paid to the occurrence of the above adverse events in association with the use of daratumumab. PMDA also concluded, however, that further safety information should be collected after the market launch because clinical experience with daratumumab in Japanese patients is very limited [see Section 7.R.7].

7.R.3.1 Safety profile of daratumumab

The applicant's explanation about the safety profile of daratumumab based on the safety data observed in Study 3003 (data cutoff date of March 7, 2016) and Study 3004 (data cutoff date of January 11, 2016).

The safety in Studies 3003 and 3004 is summarized in Table 24.

Table24. Outline of safety (Studies 3003 and 3004)

	Number of patients (%)			
	Study 3003		Study 3004	
	Daratumumab/Ld N = 283	Ld N = 281	Daratumumab/Bd N = 243	Bd N = 237
All adverse events	278 (98.2)	274 (97.5)	240 (98.8)	226 (95.4)
Adverse events, ≥Grade 3	229 (80.9)	207 (73.7)	185 (76.1)	150 (63.3)
Adverse events leading to death	12 (4.2)	16 (5.7)	13 (5.3)	13 (5.5)
Serious adverse events	138 (48.8)	118 (42.0)	102 (42.0)	80 (33.8)
Adverse events leading to treatment discontinuation*1	38 (13.4)	36 (12.8)	36 (14.8)	39 (16.5)
Adverse events leading to interruption	208 (73.5)	132 (47.0)	155 (63.8)	111 (46.8)
Adverse events leading to dose reduction*2	158 (55.8)	129 (45.9)	111 (45.7)	91 (38.4)

*1 Discontinuation of any of the study drugs including daratumumab.
*2 A dose reduction of at least one of lenalidomide, BTZ, and DEX. No dose reduction criteria were defined for daratumumab.

In Study 3003, adverse events occurring in the daratumumab/Ld group with an incidence of ≥10% higher than that in the Ld group were neutropenia (168 patients [59.4%] in the daratumumab/Ld group, 121 patients [43.1%] in the Ld group), diarrhoea (121 [42.8%], 69 [24.6%]), upper respiratory tract infection (90 [31.8%], 58 [20.6%]), cough (82 [29.0%], 35 [12.5%]), and vomiting (47 [16.6%], 15 [5.3%]). Adverse events of ≥Grade 3 occurring in the daratumumab/Ld group with an incidence of ≥3% higher than that in the Ld group were neutropenia (147 patients [51.9%] in the daratumumab/Ld group, 104 patients [37.0%] in the Ld group), fatigue (18 [6.4%], 7 [2.5%]), and febrile neutropenia (16 [5.7%], 7 [2.5%]). Serious adverse events occurring in the daratumumab/Ld group with an incidence of ≥2% higher than that in the Ld group was febrile neutropenia (12 patients [4.2%] in the daratumumab/Ld group, 4 patients [1.4%]). There was no adverse event that led to discontinuation of the study drug,

occurring in the daratumumab/Ld group with an incidence of ≥2% higher than that in the Ld group. Adverse events that led to interruption of the study drug, occurring in the daratumumab/Ld group with an incidence of ≥2% higher than that in the Ld group were neutropenia (96 patients [33.9%] in the daratumumab/Ld group, 48 patients [17.1%] in the Ld group), fatigue (18 [6.4%], 3 [1.1%]), diarrhoea (19 [6.7%], 9 [3.2%]), pyrexia (13 [4.6%], 3 [1.1%]), insomnia (8 [2.8%], none), hyperglycaemia (8 [2.8%], 1 [0.4%]), nasopharyngitis (8 [2.8%], 1 [0.4%]), ALT increased (7 [2.5%], 1 [0.4%]), and nausea (6 [2.1%], none). Adverse events that led to dose reduction of study drugs, occurring in the daratumumab/Ld group with an incidence of ≥2% higher than that in the Ld group were neutropenia (57 patients [20.1%] in the daratumumab/Ld group, 40 patients [14.2%] in the Ld group), fatigue (22 [7.8%], 7 [2.5%]), renal impairment (16 [5.7%], 7 [2.5%]), muscular weakness (14 [4.9%], 7 [2.5%]), and diarrhoea (9 [3.2%], 2 [0.7%]).

In Study 3004, adverse events occurring in the daratumumab/Bd group with an incidence of ≥10% higher than that in the Bd group were thrombocytopenia (143 patients [58.8%] in the daratumumab/Bd group, 104 patients [43.9%] in the Bd group) and cough (58 [23.9%], 30 [12.7%]). Adverse events of ≥Grade 3 occurring in the daratumumab/Bd group with an incidence of ≥3% higher than that in the Bd group were thrombocytopenia (110 patients [45.3%] in the daratumumab/Bd group, 78 patients [32.9%] in the Bd group), neutropenia (31 [12.8%], 10 [4.2%]), lymphopenia (23 [9.5%], 6 [2.5%]), and hypertension (16 [6.6%], 2 [0.8%]). Serious adverse events occurring in the daratumumab/Bd group with an incidence of ≥2% higher than that in the Bd group were anaemia (8 patients [3.3%] in the daratumumab/Bd group, 1 patient [0.4%] in the Bd group), thrombocytopenia (6 [2.5%], 1 [0.4%]), and atrial fibrillation (5 [2.1%], none). There was no adverse event that led to discontinuation of the study drug, occurring in the daratumumab/Bd group with an incidence of ≥2% higher than that in the Bd group. Adverse events that led to interruption of the study drug, occurring in the daratumumab/Bd group with an incidence of ≥2% higher than that in the Bd group were thrombocytopenia (39 patients [16.0%] in the daratumumab/Bd group, 20 patients [8.4%] in the Bd group), diarrhoea (17 [7.0%], 3 [1.3%]), peripheral sensory neuropathy (51 [21.0%], 41 [17.3%]), pyrexia (9 [3.7%], 2 [0.8%]), neutropenia (6 [2.5%], 1 [0.4%]), pneumonia (14 [5.8%], 9 [3.8%]), and bronchitis (8 [3.3%], 3 [1.3%]). An adverse event that led to dose reduction of study drugs, occurring in the daratumumab/Bd group with an incidence of ≥2% higher than that in the Bd group was peripheral sensory neuropathy (64 patients [26.3%] in the daratumumab/Bd group, 45 patients [19.0%] in the Bd group).

PMDA's review and discussion:
Adverse events occurring more frequently in the daratumumab groups than in the control groups in Studies 3003 and 3004 require attention as adverse events associated with the use of daratumumab, and information on the occurrence of these adverse events should be appropriately provided to the healthcare professionals in clinical practice.

7.R.3.2 Differences in safety between Japanese and non-Japanese patients

The applicant's explanation on the differences in the safety of daratumumab between Japanese and non-

Japanese patients, based on the safety data from Studies 3003, 3004, and 1005:

The safety of daratumumab in Japanese and non-Japanese patients in Study 3003 is summarized in Table 25.

Table 25. Outline of differences in safety between Japanese and non-Japanese patients (Study 3003)

	Number of patients (%)			
	Japanese patients		Non-Japanese patients	
	Daratumumab/Ld N = 20	Ld N = 15	Daratumumab/Ld N = 263	Ld N = 266
All adverse events	20 (100)	15 (100)	258 (98.1)	259 (97.4)
Adverse events, ≥Grade 3	19 (95.0)	12 (80.0)	210 (79.8)	195 (73.3)
Adverse events leading to death	0	1 (6.7)	12 (4.6)	15 (5.6)
Serious adverse events	7 (35.0)	3 (20.0)	131 (49.8)	115 (43.2)
Adverse events leading to treatment discontinuation*1	2 (10.0)	0	17 (6.5)	22 (8.3)
Adverse events leading to interruption	19 (95.0)	9 (60.0)	189 (71.9)	123 (46.2)
Adverse events leading to dose reduction*2	16 (80.0)	7 (46.7)	142 (54.0)	122 (45.9)

*1 Discontinuation of any of the study drugs including daratumumab.

*2 A dose reduction of either or both lenalidomide and DEX. No dose reduction criteria were defined for daratumumab.

In the daratumumab/Ld group of Study 3003, adverse events occurring in Japanese patients with an incidence of ≥15% higher than that in non-Japanese patients were nasopharyngitis (9 Japanese patients [45.0%], 59 non-Japanese patients [22.4%]), lymphopenia (8 Japanese patients [40.0%], 9 non-Japanese patients [3.4%]), and ALT increased (5 Japanese patients [25.0%], 10 non-Japanese patients [3.8%]). Grade 3 or higher adverse events occurring in Japanese patients with an incidence of ≥10% higher than that in non-Japanese patients were lymphopenia (8 Japanese patients [40.0%], 7 non-Japanese patients [2.7%]) and ALT increased (3 Japanese patients [15.0%], 4 non-Japanese patients [1.5%]). Among adverse events leading to interruption of the study drug, those occurring in Japanese patients with an incidence of ≥10% higher than that in non-Japanese patients were lymphopenia (2 Japanese patients [10.0%] versus no non-Japanese patients) and ALT increased (3 Japanese patients [15.0%] versus 4 non-Japanese patients [1.5%]). There was no serious adverse event, adverse event leading to study drug discontinuation, and adverse event leading to dose reduction of the study drug that occurred in Japanese patients with an incidence of ≥10% higher than in non-Japanese patients.

The safety of daratumumab in Study 1005 conducted in Japanese patients and Study 3004 conducted in non-Japanese patients is summarized in Table 26.

Table 26. Outline of differences in safety between Japanese and non-Japanese patients (Studies 1005 and 3004)

	Number of patients (%)	
	Study 1005 N = 8	Study 3004: Daratumumab/Bd N = 243
All adverse events	8 (100)	240 (98.8)
Adverse events, ≥Grade 3	8 (100)	185 (76.1)
Adverse events leading to death	0	13 (5.3)
Serious adverse events	3 (37.5)	102 (42.0)
Adverse events leading to treatment discontinuation*1	1 (12.5)	18 (7.4)
Adverse events leading to interruption	7 (87.5)	155 (63.8)
Adverse events leading to dose reduction*2	8 (100)	111 (45.7)

*1 Discontinuation of any of the study drugs including daratumumab.

*2 A dose reduction of either or both of BTZ and DEX. No dose reduction criteria were defined for daratumumab.

Adverse events occurring in Study 1005 with an incidence of ≥15% higher than that in the daratumumab/Bd group in Study 3004 were thrombocytopenia (7 patients [87.5%] in Study 1005, 143 patients [58.8%] in the daratumumab/Bd group in Study 3004), lymphopenia (5 [62.5%], 32 [13.2%]), leukopenia (3 [37.5%], 19 [7.8%]), neutropenia (3 [37.5%], 43 [17.7%]), fatigue (3 [37.5%], 52 [21.4%]), chills (2 [25.0%], 11 [4.5%]), hyperglycaemia (3 [37.5%], 21 [8.6%]), dehydration (2 [25.0%], 3 [1.2%]), dysaesthesia (3 [37.5%], 2 [0.8%]), gastritis (2 [25.0%], 4 [1.6%]), LDH increased (3 [37.5%], 3 [1.2%]), weight decreased (3 [37.5%], 13 [5.3%]), hypoxia (2 [25.0%], none), wheezing (2 [25.0%], 5 [2.1%]), nasopharyngitis (2 [25.0%], 17 [7.0%]), and hypokalaemia (2 [25.0%], 22 [9.1%]). Grade 3 or higher adverse events occurring in ≥2 patients in Study 1005 with an incidence of ≥10% higher than that in the daratumumab/Bd group in Study 3004 were platelet count decreased (6 patients [75.0%] in Study 1005, 110 patients [45.3%] in the daratumumab/Bd group in Study 3004), lymphopenia (5 [62.5%], 23 [9.5%]), leukopenia (2 [25.0%], 5 [2.1%]), neutropenia (2 [25.0%], 31 [12.8%]), hyperglycaemia (2 [25.0%], 8 [3.3%]), and hypokalaemia (2 [25.0%], 6 [2.5%]). An adverse event leading to interruption of study drugs and occurring in ≥2 patients in Study 1005 with an incidence of ≥10% higher than that in the daratumumab/Bd group in Study 3004 was platelet count decreased (3 patients [37.5%] in Study 1005, 39 patients [16.0%] in the daratumumab/Bd group in Study 3004). Among adverse events leading to dose reduction of study drugs, those occurring in ≥2 patients in Study 1005 with an incidence of ≥10% higher than that in the daratumumab/Bd group in Study 3004 were platelet count decreased (2 patients [25.0%] in Study 1005, 23 patients [9.5%] in the daratumumab/Bd group in Study 3004) and hyperglycaemia (2 [25.0%], 3 [1.2%]). Among serious adverse events and adverse events leading to discontinuation of the study drug, there was no adverse event that occurred in ≥2 Japanese patients with an incidence higher than in non-Japanese patients.

PMDA's review and discussion:

Because of the limited number of Japanese patients, it is difficult to draw a definitive conclusion on the differences in the safety profiles of daratumumab between Japanese and non-Japanese patients based on data from Studies 3003, 3004, and 1005. However, attention should be paid to ≥Grade 3 adverse events occurring more frequently in Japanese patients than in non-Japanese patients, and the occurrence of

these adverse events should be communicated to healthcare professionals in clinical practice by using documents and materials. In consideration of the limited safety information for daratumumab in Japanese patients, PMDA concluded that information should be continued to be collected after the market launch, and information should be provided properly to healthcare professionals in clinical practice if any new findings are found.

In the sections below, PMDA discusses adverse events especially focusing on ≥Grade 3 adverse events or serious adverse events occurring more frequently in the daratumumab group than in control groups, adverse events occurring more frequently in Japanese patients than in non-Japanese patients, and adverse events for which precautions are provided in the foreign package inserts.

7.R.3.3 Infusion reactions

(a) The occurrence of infusion reaction and its time of occurrence:

The applicant's explanation on the occurrence of infusion reactions in association with the use of daratumumab:

Adverse events which occurred during the period from the start of daratumumab treatment to the following day of the treatment and were coded with 131 MedDRA (MedDRA/J ver. 18.0) PT terms[35)] were counted.

Infusion reactions observed in Studies 3003 and 3004 are shown in Tables 27 and 28, respectively.

[35)] Cough, productive cough, allergic cough, dyspnoea, throat tightness, throat irritation, larynx irritation, nasal congestion, bronchospasm, rhinitis allergic, wheezing, oropharyngeal swelling, pharyngeal oedema, laryngeal oedema, rhinorrhoea, sneezing, hypoxia, oropharyngeal pain, dysphonia, nasal obstruction, allergic respiratory symptom, asphyxia, asthma, haemoptysis, laryngeal discomfort, laryngeal stenosis, laryngitis allergic, nasal discomfort, nasal disorder, oropharyngeal discomfort, paranasal sinus discomfort, prolonged expiration, pulmonary oedema, respiratory tract congestion, rhonchi, sinus congestion, sinus disorder, stridor, suffocation feeling, upper-airway cough syndrome, chills, pyrexia, chest discomfort, feeling cold, fatigue, non-cardiac chest pain, influenza like illness, hyperthermia, pain, chest pain, extravasation, infusion site bruising, infusion site pruritus, infusion site rash, malaise, oedema mucosal, secretion discharge, sense of oppression, nausea, vomiting, diarrhoea, abdominal pain, dysphagia, paraesthesia oral, abdominal pain upper, lip swelling, dyspepsia, lip pruritus, odynophagia, palatal oedema, tongue pruritus, hypertension, blood pressure increased, flushing, hypotension, hot flush, vasodilatation, pruritus, rash, rash erythematous, rash maculo-papular, rash pruritic, rash macular, hyperhidrosis, urticaria, erythema, dermatitis allergic, cold sweat, erythema multiforme, pruritus allergic, swelling face, lacrimation increased, conjunctival oedema, eye irritation, eye pruritus, eye swelling, vision blurred, eye allergy, eye discharge, eye disorder, eyelid oedema, ocular hyperaemia, headache, dizziness, paraesthesia, dysgeusia, speech disorder, syncope, sinus tachycardia, tachycardia, angina pectoris, palpitations, supraventricular tachycardia, bradycardia, back pain, musculoskeletal chest pain, myalgia, bone pain, musculoskeletal pain, cytokine release syndrome, drug hypersensitivity, seasonal allergy, ear pruritus, vertigo, electrocardiogram QT prolonged, heart rate increased, oxygen saturation decreased, anxiety, delirium, depression, and infusion related reaction.

Table 27. Occurrence of infusion reactions with an incidence of ≥5% in either group (Study 3003)

MedDRA PT (MedDRA/J ver.18.0)	Number of patients (%)			
	Daratumumab/Ld N = 283		Ld N = 281	
	All grades	≥Grade 3	All grades	≥Grade 3
Infusion reaction	219 (77.4)	34 (12.0)	161 (57.3)	9 (3.2)
Fatigue	46 (16.3)	5 (1.8)	54 (19.2)	2 (0.7)
Cough	40 (14.1)	0	17 (6.0)	0
Dyspnoea	36 (12.7)	4 (1.4)	14 (5.0)	0
Diarrhoea	33 (11.7)	1 (0.4)	30 (10.7)	3 (1.1)
Nausea	30 (10.6)	1 (0.4)	19 (6.8)	0
Vomiting	24 (8.5)	1 (0.4)	5 (1.8)	0
Back pain	23 (8.1)	2 (0.7)	27 (9.6)	1 (0.4)
Pruritus	16 (5.7)	1 (0.4)	10 (3.6)	0
Headache	16 (5.7)	0	11 (3.9)	0
Abdominal pain upper	15 (5.3)	0	7 (2.5)	0
Rash	13 (4.6)	0	17 (6.0)	0
Dizziness	11 (3.9)	0	14 (5.0)	0

Table 28. Occurrence of infusion reactions with an incidence of ≥5% in either group (Study 3004)

MedDRA PT (MedDRA/J ver.18.0)	Number of patients (%)			
	Daratumumab/Bd N = 243		Bd N = 237	
	All grades	≥Grade 3	All grades	≥Grade 3
Infusion reaction	156 (64.2)	29 (11.9)	133 (56.1)	12 (5.1)
Dyspnoea	30 (12.3)	5 (2.1)	13 (5.5)	0
Cough	28 (11.5)	0	12 (5.1)	0
Diarrhoea	25 (10.3)	0	35 (14.8)	1 (0.4)
Bronchospasm	22 (9.1)	6 (2.5)	0	0
Fatigue	20 (8.2)	1 (0.4)	41 (17.3)	1 (0.4)
Hypertension	17 (7.0)	12 (4.9)	7 (3.0)	1 (0.4)
Nausea	16 (6.6)	0	20 (8.4)	0
Vomiting	16 (6.6)	0	7 (3.0)	0
Headache	15 (6.2)	0	8 (3.4)	0
Back pain	11 (4.5)	1 (0.4)	13 (5.5)	1 (0.4)

In Study 3003, there was no infusion reaction resulting in death or leading to discontinuation of the study drug. Serious infusion reactions occurred in 6 patients in the daratumumab/LD group (2.1%, hypertension and chest discomfort in 1 patient; back pain in 1 patient; non-cardiac chest pain in 1 patient; syncope in 1 patient; hypotension in 1 patient; and pyrexia in 1 patient) and 3 patients in the Ld group (1.1%, non-cardiac chest pain in 1 patient, pyrexia in 1 patient, and diarrhoea in 1 patient). A causal relationship to the study drug could not be ruled out for hypertension and chest discomfort in 1 patient, non-cardiac chest pain in 1 patient, hypotension in 1 patient, and syncope in 1 patient in the daratumumab/Ld group. Infusion reactions led to discontinuation of the study drug in 22 patients (7.8%) in the daratumumab/LD group and 5 patients (1.8%) in the Ld group. Infusion reactions required dose reduction in 18 patients (6.4%) in the daratumumab/Ld group and 13 patients (4.6%) in the Ld group.

In Study 3004, no infusion reaction resulted in death. Serious infusion reactions occurred in 4 patients (1.6%, pyrexia in 1 patient, hypertension in 1 patient, oropharyngeal swelling in 1 patient, and laryngeal oedema in 1 patient) in the daratumumab/Bd group and 2 patients (0.8%, back pain in 1 patient and pulmonary oedema in 1 patient) in the Bd group. A causal relationship to the study drug could not be

ruled out for pyrexia in 1 patient, hypertension in 1 patient, oropharyngeal swelling in 1 patient, and laryngeal oedema in 1 patient in the daratumumab/Bd group. Infusion reactions led to discontinuation of the study drug in 1 patient (0.4%) in the daratumumab/Bd group and 1 patient (0.4%) in the Bd group. Infusion reactions led to interruption of the study drugs in 6 patients (2.5%) in the daratumumab/Bd group and 9 patients (3.8%) in the BD group. Infusion reactions required dose reduction in 4 patients (1.6%) in the daratumumab/Bd group and 8 patients (3.4%) in the Bd group.

With regard to the time of occurrence of infusion reactions in association with the use of daratumumab, Table 29 shows the occurrence of infusion reactions by daratumumab treatment cycle in Studies 3003 and 3004. The median time (range) to the onset of infusion reaction[36)] from the start of daratumumab administration was 90 minutes (7-4,370 minutes) in Study 3003 and 80 minutes (15-1,695 minutes) in Study 3004.

Table 29. Occurrence of infusion reactions by daratumumab treatment cycle (Studies 3003 and 3004)

Timing of infusion (No. of cycle*)	Study 3003				Study 3004			
	N	Number of patients (%)			N	Number of patients (%)		
		All grades	≥Grade 3	Initial onset (All grades)		All grades	≥Grade 3	Initial onset (All grades)
1	283	181 (64.0)	18 (6.4)	181 (64.0)	243	132 (54.3)	21 (8.6)	132 (54.3)
2	275	54 (19.6)	8 (2.9)	14 (5.1)	230	39 (17.0)	3 (1.3)	7 (3.0)
3	270	25 (9.3)	2 (0.7)	1 (0.4)	221	28 (12.7)	3 (1.4)	9 (4.1)
4	263	19 (7.2)	1 (0.4)	5 (1.9)	217	8 (3.7)	0	1 (0.5)
5	259	17 (6.6)	1 (0.4)	5 (1.9)	204	8 (3.9)	1 (0.5)	1 (0.5)
6	253	29 (11.5)	0	6 (2.4)	204	11 (5.4)	1 (0.5)	1 (0.5)
≥7	252	62 (24.6)	5 (2.0)	7 (2.8)	198	25 (12.6)	4 (2.0)	5 (2.5)

* The length of a cycle was 28 days in Study 3003 and 21 days in Study 3004 (28 days in Cycle 9 and subsequent cycles) [see Sections 7.1.2.1 and 7.1.3.3 for treatment interval of daratumumab in individual studies].

(b) Infusion rate and the total volume after dilution for daratumumab administration:

The applicant's explanation on the infusion rate and the total volume after dilution for daratumumab administration:

In Part 1 of Study GEN501, infusion reactions occurred frequently in the first 4 hours after the initial dosing. In consideration of the results, different infusion rates (≥4 or ≥6 hours) and different volume after dilution (500 or 1,000 mL) were applied in Part 2 of Study GEN501 [see Section 6.2.3.1] to investigate the occurrence of infusion reactions. The lowest incidence of infusion reactions was observed in the group receiving daratumumab over ≥6 hours after dilution with normal saline to 1,000 mL. In Phase II of Study GEN503, daratumumab was administered in combination with Ld, and the occurrence of infusion reactions was compared between patients receiving the initial dose of daratumumab 16 mg/kg administered over ≥6 hours after dilution with normal saline to 1,000 mL (the standard dosing group) and patients receiving the initial dose of daratumumab 16 mg/kg administered over ≥3 hours after dilution with normal saline to 500 mL (the accelerated dosing group). The incidence of infusion reactions was higher in the accelerated dosing group (47.6% for all grades and 4.8% for

[36)] Events judged by the investigators to be infusion reactions (adverse drug reactions) to daratumumab, regardless of the time to onset, were counted.

≥Grade 3 in the standard dosing group, 72.7% for all grades and 9.1% for ≥Grade 3 in the accelerated group).

Based on the results, it was considered that the infusion rate and the total volume after dilution played an important role for the occurrence of infusion reactions. Therefore, the infusion rate and the total volume after dilution for daratumumab administration were set in Studies 3003 and 3004 as shown in Table 30.

Table 30. Infusion rate and total volume after dilution for daratumumab administration in Studies 3003 and 3004

Timing of infusion	Total volume after dilution	Infusion rate after the start of administration*1 (mL/h)			
		0-1 h	1-2 h	2-3 h	>3 h
First infusion	1,000 mL	50	100	150	200
Second infusion	500 mL*2				
Third and subsequent infusions	500 mL*2	100*3	150	200	200

*1 In the absence of infusion reaction, the rate could be escalated by 50 mL/h every 1 hour up to 200 mL/h.
*2 In the absence of ≥Grade 2 infusion reaction within 3 hours after the start of first infusion, use dilution volume of 500 mL.
*3 If the final infusion rate is ≥100 mL/h at the first and second daratumumab infusion, and no ≥Grade 2 infusion reaction occurred, the infusion rate can be started at 100 mL/h.

In Studies 3003 and 3004, the following rules were specified for the infusion rate in the case of the occurrence of infusion reactions associated with the use of daratumumab:

- If a Grade 1 to 3 infusion reaction occurred, daratumumab had to be discontinued. Daratumumab could be resumed at half the rate at which the reaction occurred: for Grade 1 or 2 infusion reactions, after the patient's condition was stable (Studies 3003 and 3004); and for Grade 3 infusion reactions, after the reaction resolved or improved to Grade 1 (Study 3003) or the reaction improved to Grade 1 or 2 within 2 hours (Study 3004). After that, the infusion rate could be determined by the investigator.
- Daratumumab had to be discontinued when Grade 3 infusion reactions occurred 3 times or a Grade 4 infusion reaction occurred (Study 3003) or Grade 3 or 4 infusion reaction occurred 3 times (Study 3004).
- Daratumumab had to be discontinued when ≥Grade 2 laryngeal edema or bronchospasm occurred, which did not respond to systemic therapy and did not resolve within 6 hours after the onset (Studies 3003 and 3004).

(c) Pre-infusion and post-infusion medications:
The applicant's explanation on pre-infusion and post-infusion medications for daratumumab treatment in Studies 3003 and 3004:
The following medications were to be administered 1 hour (for oral medications, within 1-3 hours) before daratumumab infusion in Studies 3003 and 3004.

- Corticosteroids: Intravenous or oral administration of DEX 20 mg (DEX was administered only when the drug could not be administered intravenously) or long-acting corticosteroids at equivalent

doses[37)].

- Antipyretic analgesics: Intravenous or oral administration of acetaminophen 650 to 1,000 mg[38)].
- Antihistamines: Intravenous or oral administration of diphenhydramine 25 to 50 mg or equivalent products. (Note: Intravenous administration of promethazine should be avoided.)

Meanwhile, it was specified in the protocol that DEX, one of the concomitant drugs (Ld and Bd), was to be administered on the day of daratumumab administration and the following day[39)]. Therefore, the posttreatment of corticosteroids was not specified. In consideration of the following point, however, it was specified that the following post-infusion medications should be considered for patients with mild asthma or patients with chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <80%: antihistamine on the first and second days following the administration of daratumumab; short- or long-acting inhaled beta-2 agonists; inhaled steroids or inhaled anticholinergics. Post-infusion medications including inhalation medications could be discontinued at the discretion of the investigator when no infusion reactions occurred up to the completion of the fourth dosing of daratumumab.

- Bronchospasm including that of late onset was reported in patients with a history of respiratory disease such as COPD and bronchial asthma in clinical studies conducted to evaluate daratumumab monotherapy in its early development.

Studies 3003 and 3004 were conducted with the above (b) and (c) specifications, and the tolerability of daratumumab was demonstrated in these studies. Therefore, precautionary statements for the infusion rate, total volume after dilution, measures to be taken at the occurrence of infusion reactions, and pre-infusion and post-infusion medications will be included in the Precautions for Dosage and Administration section of the package insert [see Section 7.R.6].

PMDA's review and discussion:
In Studies 3003 and 3004, infusion reactions occurred in approximately 70% of subjects in the daratumumab groups, and some infusion reactions were serious or led to treatment discontinuation. In view of these infusion reactions, caution is required when daratumumab is used. Infusion reactions occurred most frequently at the initial dosing. However, there were patients who experienced an initial infusion reaction after multiple treatment cycles and patients who experienced multiple episodes of infusion reactions. In view of these results, PMDA concluded that information on the occurrence of infusion reactions in the clinical studies, including the situation above, should be appropriately provided to healthcare professionals in clinical practice, by means of materials such as the package insert.

PMDA also concluded that appropriate precautionary statements on the infusion rate, total volume after dilution, measures to be taken at the occurrence of infusion reactions, and pre-infusion and post-infusion

37) Methylprednisolone, hydrocortisone, prednisolone, and prednisone (prednisone is unapproved in Japan).
38) In Study 3003, acetaminophen 500 to 1,000 mg was administered to Japanese patients.
39) In Study 3003, during weeks when the subject receives daratumumab, half the DEX dose (i.e., 20 mg) could be administered on the day of daratumumab administration and half the dose could be administration the day after.

medications need be included in the Precautions for Dosage and Administration section and other relevant sections in the package insert to reflect Studies 3003 and 3004 [see Section 7.R.6].

7.R.3.4 Bone marrow depression

The applicant's explanation on the occurrence of bone marrow depression in association with the use of daratumumab:

In addition to the preferred terms (PTs) for MedDRA/J (ver.18.0) under the Standardised MedDRA Query (SMQ) of "Haematopoietic cytopenias" (narrow search), PTs of "Anaemia," "Haematocrit decreased," "Haemoglobin decreased," and "Reticulocyte percentage decreased" were tabulated and analyzed as adverse events associated with bone marrow depression.

The occurrence of bone marrow depression in Studies 3003 and 3004 is shown in Tables 31 and 32, respectively.

Table 31. Occurrence of bone marrow depression (Study 3003)

MedDRA PT (MedDRA/J ver.18.0)	Number of patients (%)			
	Daratumumab/Ld N = 283		Ld N = 281	
	All grades	≥Grade 3	All grades	≥Grade 3
Bone marrow depression	199 (70.3)	162 (57.2)	178 (63.3)	141 (50.2)
Neutropenia	168 (59.4)	147 (51.9)	121 (43.1)	104 (37.0)
Anaemia	88 (31.1)	35 (12.4)	98 (34.9)	55 (19.6)
Thrombocytopenia	76 (26.9)	36 (12.7)	77 (27.4)	38 (13.5)
Leukopenia	21 (7.4)	8 (2.8)	17 (6.0)	7 (2.5)
Lymphopenia	17 (6.0)	15 (5.3)	15 (5.3)	10 (3.6)
Febrile neutropenia	16 (5.7)	16 (5.7)	7 (2.5)	7 (2.5)
Bone marrow failure	0	0	1 (0.4)	1 (0.4)
Microcytic anaemia	0	0	1 (0.4)	0
Neutropenic sepsis	2 (0.7)	2 (0.7)	0	0

Table 32. Occurrence of bone marrow depression (Study 3004)

MedDRA PT (MedDRA/J ver.18.0)	Number of patients (%)			
	Daratumumab/Bd N = 243		Bd N = 237	
	All grades	≥Grade 3	All grades	≥Grade 3
Bone marrow depression	163 (67.1)	131 (53.9)	132 (55.7)	94 (39.7)
Thrombocytopenia	143 (58.8)	110 (45.3)	104 (43.9)	78 (32.9)
Anaemia	64 (26.3)	35 (14.4)	74 (31.2)	38 (16.0)
Neutropenia	43 (17.7)	31 (12.8)	22 (9.3)	10 (4.2)
Lymphopenia	32 (13.2)	23 (9.5)	9 (3.8)	6 (2.5)
Leukopenia	19 (7.8)	5 (2.1)	11 (4.6)	4 (1.7)
Febrile neutropenia	4 (1.6)	4 (1.6)	1 (0.4)	1 (0.4)

In Study 3003, no bone marrow depression with a fatal outcome was observed. Serious bone marrow depression occurred in 18 patients in the Daratumumab/Ld group (6.4%; febrile neutropenia in 12, anaemia in 2, neutropenia in 2, thrombocytopenia in 1, and neutropenic sepsis in 1) and 7 patients in the Ld group (2.5%; febrile neutropenia in 3, anaemia in 2, febrile neutropenia and thrombocytopenia in 1, and bone marrow failure in 1). A causal relationship to the study drug could not be ruled out for febrile neutropenia in 3 patients in the daratumumab/Ld group, febrile neutropenia in 3 patients, febrile

neutropenia and thrombocytopenia in 1 patient, and anemia in 1 patient in the Ld group. Bone marrow depression leading to discontinuation of the study drug occurred in none in the daratumumab/Ld group and 2 patients (0.7%) in the Ld group. Bone marrow depression leading to interruption of the study drug occurred in 103 patients (36.4%) in the daratumumab/Ld group and 61 patients (21.7%) in the Ld group. Bone marrow depression leading to dose reduction occurred in 70 patients (24.7%) in the daratumumab/Ld group and 51 patients (18.1%) in the Ld group.

In Study 3004, there was no bone marrow depression that led to death or discontinuation of the study drug. Serious bone marrow depression occurred in 15 patients (6.2%; anaemia in 7; thrombocytopenia in 5; febrile neutropenia, anemia, thrombocytopenia, and neutropenia in 1; febrile neutropenia in 1; and neutropenia in 1) in the daratumumab/Bd group and 2 patients (0.8%; anaemia in 1 and thrombocytopenia in 1) in the Bd group. Among these events, a causal relationship to the study drug could not be ruled out for anaemia in 4 patients and thrombocytopenia in 4 patients in the daratumumab/Bd group and thrombocytopenia in 1 patient in the Bd group. Bone marrow depression leading to interruption of study drugs occurred in 41 patients (16.9%) in the daratumumab/Bd group and 22 patients (9.3%) in the Bd group. Bone marrow depression leading to dose reduction of study drugs occurred in 23 patients (9.5%) in the daratumumab/Bd group and 21 patients (8.9%) in the Bd group.

PMDA's review and discussion:
In Studies 3003 and 3004, bone marrow depressions such as ≥Grade 3 neutropenia, thrombocytopenia, and lymphopenia occurred more frequently in the daratumumab groups than the control groups, and serious bone marrow depressions for which a causal relationship to daratumumab cannot be denied have been reported. Taking account of the above, caution is needed during the use of daratumumab. Therefore, PMDA concluded the followings: information on the occurrence of bone marrow depression observed in the clinical studies should be provided to healthcare professionals in clinical practice, by means of materials such as the package insert; hematological tests should be performed on a regular basis during the use of daratumumab, and precautions should be properly provided to healthcare professionals so that they can take appropriate measures (e.g., interruption and dose reduction of daratumumab and concomitant drugs) in the case of abnormal test results.

7.R.3.5 Infections

The applicant's explanation on the occurrence of infections in association with the use of daratumumab:
The PTs under the MedDRA SOC (MedDRA/J ver.18.0) of "Infections and infestations" were tabulated and analyzed as adverse events associated with infections.

The occurrence of infections in Studies 3003 and 3004 is shown in Tables 33 and 34, respectively.

Table 33. Infections with an incidence of ≥2% in either group (Study 3003)

MedDRA PT (MedDRA/J ver.18.0)	Number of patients (%)			
	Daratumumab/Ld N = 283		Ld N = 281	
	All grades	≥Grade 3	All grades	≥Grade 3
Infections	238 (84.1)	82 (29.0)	204 (72.6)	64 (22.8)
Upper respiratory tract infection	90 (31.8)	3 (1.1)	58 (20.6)	3 (1.1)
Nasopharyngitis	68 (24.0)	0	43 (15.3)	0
Pneumonia	40 (14.1)	22 (7.8)	37 (13.2)	23 (8.2)
Bronchitis	38 (13.4)	4 (1.4)	34 (12.1)	6 (2.1)
Respiratory tract infection	31 (11.0)	5 (1.8)	22 (7.8)	2 (0.7)
Influenza	21 (7.4)	8 (2.8)	13 (4.6)	2 (0.7)
Sinusitis	18 (6.4)	0	10 (3.6)	0
Lower respiratory tract infection	17 (6.0)	5 (1.8)	9 (3.2)	3 (1.1)
Urinary tract infection	15 (5.3)	5 (1.8)	11 (3.9)	1 (0.4)
Rhinitis	15 (5.3)	0	3 (1.1)	0
Conjunctivitis	11 (3.9)	0	3 (1.1)	0
Gastroenteritis	10 (3.5)	1 (0.4)	4 (1.4)	0
Herpes zoster	6 (2.1)	0	5 (1.8)	1 (0.4)
Oral candidiasis	6 (2.1)	0	4 (1.4)	0
Oral herpes	6 (2.1)	0	2 (0.7)	0
Viral infection	5 (1.8)	0	7 (2.5)	0
Pharyngitis	4 (1.4)	0	7 (2.5)	1 (0.4)
Cystitis	4 (1.4)	0	7 (2.5)	0
Sepsis	2 (0.7)	2 (0.7)	6 (2.1)	6 (2.1)
Tooth abscess	2 (0.7)	0	6 (2.1)	0

Table 34. Infections with an incidence of ≥2% in either group (Study 3004)

MedDRA PT (MedDRA/J ver.18.0)	Number of patients (%)			
	Daratumumab/Bd N = 243		Bd N = 237	
	All grades	≥Grade 3	All grades	≥Grade 3
Infections	164 (67.5)	52 (21.4)	126 (53.2)	46 (19.4)
Upper respiratory tract infection	60 (24.7)	4 (1.6)	43 (18.1)	2 (0.8)
Pneumonia	29 (11.9)	20 (8.2)	28 (11.8)	23 (9.7)
Bronchitis	28 (11.5)	5 (2.1)	13 (5.5)	3 (1.3)
Conjunctivitis	21 (8.6)	0	7 (3.0)	1 (0.4)
Nasopharyngitis	17 (7.0)	0	9 (3.8)	0
Herpes zoster	13 (5.3)	4 (1.6)	7 (3.0)	1 (0.4)
Urinary tract infection	12 (4.9)	1 (0.4)	6 (2.5)	1 (0.4)
Sinusitis	10 (4.1)	3 (1.2)	3 (1.3)	0
Influenza	8 (3.3)	1 (0.4)	7 (3.0)	2 (0.8)
Rhinitis	7 (2.9)	0	2 (0.8)	0
Respiratory tract infection viral	6 (2.5)	0	3 (1.3)	0
Oral herpes	6 (2.5)	0	2 (0.8)	0
Gastroenteritis	5 (2.1)	2 (0.8)	4 (1.7)	3 (1.3)
Pharyngitis	5 (2.1)	0	1 (0.4)	0
Oral candidiasis	4 (1.6)	0	5 (2.1)	0

In Study 3003, infections led to death in 6 patients (2.1%; septic shock in 3, pneumonia in 2, and pneumonia bacterial 1) in the daratumumab/Ld group and 4 patients (1.4%; pneumonia in 2, septic shock in 1, and sepsis in 1) in the Ld group. Among these events, a causal relationship to the study drug could not be ruled out for pneumonia in 2 patients, septic shock in 1 patient, and pneumonia bacterial in 1 patient in the daratumumab/Ld group. Serious infections occurred in 85 patients (30.0%; serious infection events observed in ≥5 patients included pneumonia in 23, influenza in 8, lower respiratory tract infection in 7, bronchitis in 5, and respiratory tract infection in 5) in the daratumumab/Ld group

and 64 patients (22.8%; serious infection events observed in ≥5 patients included pneumonia in 24, sepsis in 5, and upper respiratory tract infection in 5) in the Ld group. Among these events, a causal relationship to the study drug could not be ruled out for pneumonia in 15 patients, lower respiratory tract infection in 5, influenza in 2, and respiratory tract infection in 1 in the daratumumab/Ld group and pneumonia in 9, upper respiratory tract infection in 3, and sepsis in 1 in the Ld group. Infections led to discontinuation of the study drug in 7 patients (2.5%) in the daratumumab/Ld group and 5 patients (1.8%) in the Ld group. Infections led to the interruption of the study drug in 89 patients (31.4%) in the daratumumab/Ld group and 53 patients (18.9%) in the Ld group. Infections led dose reduction of the study drug in 10 patients (3.5%) in the daratumumab/Ld group and 4 patients (1.4%) in the Ld group.

In Study 3004, infections led to death in 1 patient (0.4%, pneumonia) in the daratumumab/Bd group and 4 patients (1.7%; pneumonia in 2, septic shock in 1, and tracheobronchitis in 1) in the Bd group. Among these events, a causal relationship to the study drug could not be ruled out for pneumonia in 1 patient in the daratumumab/Bd group and pneumonia in 1 patient and tracheobronchitis in 1 in the Bd group. Serious infections occurred in 48 patients (19.8%; serious infection events observed in ≥5 patients included pneumonia in 19 patients and bronchitis in 5) in the daratumumab/Bd group and 43 patients (18.1%; a serious infection event observed in ≥5 patients included pneumonia in 22 patients) in the Bd group. Among these events, a causal relationship to the study drug could not be ruled out for pneumonia in 10 patients and bronchitis in 3 patients in the daratumumab/Bd group and pneumonia in 13 patients in the Bd group. Infections led to discontinuation of the study drug in 6 patients (2.5%) in the daratumumab/Bd group and 5 patients (2.1%) in the Bd group. Infections led to the interruption of the study drug in 56 patients (23.0%) in the daratumumab/Bd group and 39 patients (16.5%) in the Bd group. Infections required dose reduction of the study drug in 5 patients (2.1%) in the daratumumab/Bd group and 9 patients (3.8%) in the Bd group.

PMDA asked the applicant to describe the following: 1) the implementation status on screening and monitoring of opportunistic infections (caused by cytomegalovirus [CMV], tubercle bacillus, herpes zoster virus, etc.) and hepatitis B virus [HBV]; and 2) specification of prophylaxis against opportunistic infections and its implementation status.

The applicant's response:
1) It was specified that patients were excluded if they were seropositive for hepatitis B surface (HBs) antigens as a result of HBV screening. No other specifications were made.

2) Prophylaxis against *Pneumocystis jirovecii* and herpes zoster virus was recommended.[40)] The occurrence of and the implementation status of prophylaxis against opportunistic infections are described below.

[40)] Regarding *Pneumocystis jirovecii*, it was specified that prophylaxis against pneumocystis pneumonia should be considered in accordance with guidelines used in the individual study sites. Regarding herpes zoster virus, it was recommended that well-tolerable antivirals (e.g., aciclovir and valaciclovir) be started not later than 1 week after the start of administration of the study drug during treatment period to prevent recurrence of herpes zoster.

- CMV infection: Prophylaxis was provided to 180 of 283 patients (63.6%) in the daratumumab/Ld group and 128 of 281 patients (45.6%) in the Ld group in Study 3003 and to 188 of 243 patients (77.4%) in the daratumumab/Bd group and 188 of 237 patients (79.3%) in the Bd group in Study 3004. Among patients vaccinated, CMV infections were reported in 1 of 180 patients (0.6%) in the daratumumab/Ld group and none of 128 patients in the Ld group in Study 3003 and 2 of 188 patients (1.1%) in the daratumumab/Bd group and none of 188 patients in the Bd group in Study 3004. No CMV infection was reported in unvaccinated patients.
- Tuberculous infection: Prophylaxis was provided to 1 of 283 patients (0.4%) in the daratumumab/Ld group and 1 of 281 patients (0.4%) in the Ld group in Study 3003. No tuberculous infection was reported from the vaccinated patients. Among unvaccinated patients, tuberculous infection was reported in none of 282 patients in the daratumumab/Ld group and 1 of 280 patients (0.4%) in the Ld group. In Study 3004, no patients received prophylaxis against tubercle bacillus, and no tuberculous infection was observed.
- *Pneumocystis jirovecii* infection: Prophylaxis was provided to 110 of 283 patients (38.9%) in the daratumumab/Ld group and 99 of 281 patients (35.2%) in the Ld group in Study 3003 and 105 of 243 patients (43.2%) in the daratumumab/Bd group and 93 of 237 patients (39.2%) in the Bd group in Study 3004. No pneumocystis jirovecii infection occurred in the vaccinated patients. Among unvaccinated patients, *Pneumocystis jirovecii* infection was reported in 1 of 138 patients (0.7%) in the daratumumab/Bd group and none of 144 patients in the Bd group in Study 3004.
- Herpes zoster virus infection: Prophylaxis was provided to 178 of 283 patients (62.9%) in the daratumumab/Ld group and 128 of 281 patients (45.6%) in the Ld group in Study 3003 and 187 of 243 patients (77.0%) in the daratumumab/Bd group and 186 of 237 patients (78.5%) in the Bd group in Study 3004. Among vaccinated patients, herpes zoster virus infection occurred in 1 of 178 patients (0.6%) in the daratumumab/Ld group and 1 of 128 patients (0.8%) in the Ld group in Study 3003 and 8 of 187 patients (4.3%) in the daratumumab/Bd group and 1 of 186 patients (0.5%) in the Bd group in Study 3004. Among unvaccinated patients, herpes zoster virus infection occurred in 5 of 105 patients (4.8%) in the daratumumab/Ld group and 4 of 153 patients (2.6%) in the Ld group in Study 3003 and 5 of 56 patients (8.9%) in the daratumumab/Bd group and 6 of 51 patients (11.8%) in the Bd group in Study 3004.

PMDA's review and discussion:

In Studies 3003 and 3004, serious infections or infections leading to death for which a causal relationship to daratumumab could not be denied occurred in multiple patients. Taking account of the above, caution is needed during the use of daratumumab. Therefore, PMDA concluded the followings: information on the occurrence of infections observed in the clinical studies should be provided to healthcare professionals in clinical practice, by means of materials such as the package insert; and details of safety measures taken against infections in the above-mentioned clinical studies should also be provided appropriately to healthcare professionals in clinical practice, by means of materials.

7.R.3.6 Haemolysis

The applicant's explanation on the occurrence of haemolysis:

The following MedDRA PTs (MedDRA/J ver.18.0) were tabulated and analyzed as adverse events related to haemolysis: Warm type haemolytic anaemia; intravascular haemolysis; haemolytic transfusion reaction; haemolytic uraemic syndrome; haemolytic anaemia; haemolytic icteroanaemia; haemolysis; extravascular haemolysis; delayed haemolytic transfusion reaction; Coombs positive haemolytic anaemia; cold type haemolytic anaemia; autoimmune haemolytic anaemia; and acute haemolytic transfusion reaction.

Among the clinical studies submitted, haemolysis (Grade 1, non-serious) was reported in 1 patient receiving daratumumab in combination with Pd in Study 1001 and its causal relationship to daratumumab could not be ruled out. In this patient, haemolysis occurred 12 days after the last dose of daratumumab (13 days after the last blood transfusion).

In the post-marketing experiences outside Japan (the data cutoff date of March 16, 2017), 4 events of serious or ≥Grade 3 haemolysis were reported: haemolysis (2 events), haemolytic anaemia (1), and intravascular haemolysis (1). All of these events were reported as serious.

The above data on the occurrence of haemolysis does not allow us to draw a definite conclusion on the relationship between daratumumab and haemolysis. However, taking into account that daratumumab is an antibody product which reacts with the epitope on the extracellular region of CD38, the possibility cannot be ruled out that binding of daratumumab to CD38 expressed on the surface of red blood cells may cause haemolysis. Therefore, information on the occurrence of haemolysis in clinical studies or other settings should be appropriately provided to healthcare professionals in clinical practice by means of materials.

PMDA accepted the applicant's explanation.

7.R.4 Interference with laboratory tests

(a) Effects of daratumumab on response evaluation:

Since daratumumab is an IgG1κ monoclonal antibody that can be detected on both the serum protein electrophoresis and immunofixation assays used for measurement of M-protein, PMDA asked the applicant to explain the possible impact of daratumumab on the measurement and determination of determination of best overall response and to discuss the necessity of precautions concerning the impact thereof.

The applicant's response:

In Studies 3003 and 3004, it was specified that testing with daratumumab-specific immunofixation reflex assay (DIRA) was to be performed in the case of the following, and DIRAs were performed in 95 of 286 patients (33.2%) in the daratumumab/Ld group of Study 3003 and 50 of 251 patients (19.9%) in

the daratumumab/Bd group of Study 3004.

- Required at the investigator's discretion
- Serum monoclonal paraprotein (M-protein) level is ≤0.2 g/dL on serum protein electrophoresis at ≥2 consecutive measurements in a patient with IgG-κ type MM
- Serum M-protein level is 0 on serum protein electrophoresis but ≥2 consecutive positive results for IgG antibody.

In Study 3003, DIRAs were performed in patients who were determined to have VGPR before receiving DIRA assay. The repeated test demonstrated negative conversion in some patients, and their response was changed to sCR in 2 patients and to CR in 4 patients. In Study 3004, no response was changed. The effects of daratumumab on the serum M-protein quantitation are small even when daratumumab impacts the measurements of serum protein electrophoresis or immunofixation. Accordingly, responses other than CR and sCR can be determined by these assays. Nevertheless, since the information that daratumumab may influence the determination of CR and sCR is useful for precise determination of patients' response to therapy, precautions concerning the possible interference are provided properly to healthcare professionals in clinical practice, by means of materials such as the package insert.

(b) Interference with indirect Coombs test and effects on blood transfusion:
Daratumumab binds to CD38 expressed at low levels on red blood cells and may result in a positive indirect Coombs test, which in turn may make it difficult to precisely determine the presence or absence of irregular antibodies in patients receiving daratumumab. The applicant provided the following explanation regarding the occurrence of and measures taken for adverse events related to the interference of daratumumab with indirect Coombs test and the effects of daratumumab on blood transfusion.

The applicant's explanation:
The following MedDRA PTs (MedDRA/J ver.18.0) were tabulated and analyzed as adverse events related to the interference with indirect Coombs test and the effects on blood transfusion: Coombs indirect test; Coombs indirect test positive; crossmatch incompatible; and laboratory test interference.

In clinical studies conducted in and outside of Japan, adverse events related to the interference with indirect Coombs test and the effects on blood transfusion occurred in 3 patients (crossmatch incompatible) in the 16 mg/kg treatment group in Study GEN501 and in 1 patient (laboratory test interference) in the daratumumab/Bd group in Study 1001. Haemolysis after blood transfusion was not observed in any of the patients with the events, but these patients could not receive the transfusion of a matched blood product. The adverse events were considered to be medically significant and thus determined to be serious. In the overseas post-marketing experiences outside Japan (the data cutoff date of March 16, 2017), 16 events related to the interference with indirect Coombs test and effects on blood transfusion were reported: 11 events of crossmatch incompatible and 5 events of laboratory test interference. At present, no case of haemolysis or a relevant adverse event has been reported as a result of the interference of daratumumab with Coombs test after blood transfusion.

Reported mitigation methods for daratumumab interference with indirect Coombs test include dithiothreitol (DTT) treatment to disrupt daratumumab binding to CD38 on red blood cells (*Transfusion.* 2015;55:1545-54; and the Guidelines for pre-transfusion compatibility procedures in blood transfusion laboratories in Japan [2nd edition], the Japan Society of Transfusion Medicine and Cell Therapy eds.) and phenotyping/genotyping to determine the phenotype or genotype of blood (*Transfusion.* 2015;55:2770). DTT treatment has been validated in clinical studies (*Transfusion.* 2016;56:2964-72). However, since Kell antigens are degenerated by DTT treatment, Kell antibodies cannot be evaluated in irregular antibody screenings. Accordingly, when irregular antibodies are screened by using DTT, Kell antibody-negative blood product should be supplied. In addition, general pre-transfusion tests, including irregular antibody screening, should be performed before the administration of daratumumab even in patients not scheduled for transfusion.

Information on the daratumumab interference with direct Coombs test is particularly important when providing blood transfusion to patients who are receiving daratumumab or have completed daratumumab treatment. If the information on exposure to daratumumab is not shared, it may result in a risk of delayed blood transfusion. Therefore, precautions concerning the impact of daratumumab on indirect Coombs test and the necessity of implementation of pre-transfusion test before daratumumab treatment should be provided to healthcare professionals including persons in blood transfusion test segments, patients, and specialized institutions for blood transfusion, by means of materials including the package insert.

PMDA accepted the applicant's explanation on the above (a) and (b).

7.R.5 Clinical positioning and indication

Daratumumab was proposed to be indicated for "the treatment of relapsed or refractory multiple myeloma." The following precautions were also proposed to be included in the Precautions for Indications section of the package insert.

- Daratumumab should be used in patients with MM who failed to respond to at least one prior standard therapy or who had relapsed MM after the therapy.
- Physicians should select appropriate patients after thoroughly understanding the details of the clinical study patients, including previous treatment history, described in the Clinical Studies section of the package insert and fully understanding the efficacy and safety profiles of daratumumab.

As a result of its review shown below and in Sections "7.R.2 Efficacy" and "7.R.3 Safety," PMDA concluded that the instructions and precautions in the Indication and Precautions for Indications sections of the package insert should be described as proposed.

7.R.5.1 Clinical positioning of daratumumab

Daratumumab for treatment of relapsed and refractory MM is described as follows in the Japanese and non-Japanese treatment guidelines and the standard textbooks of hematology and clinical oncology.

Treatment guidelines:

- NCCN Guidelines (v3.2017): For patients with relapsed and refractory MM, daratumumab/Ld or daratumumab/Bd is recommended [Category 1[41)]] and daratumumab monotherapy is also recommended [Category 2A[42)]].
- The US NCI-PDQ (February 3, 2017): The overall response rate for daratumumab as a single agent for relapsed or refractory MM was 36%. Responders had an 80% OS at 2 years. [Level of evidence: 3iiiDiv[43)]].
- Guidelines for Treatment of Multiple Myeloma (4th edition), the Japanese Society of Myeloma ed. (Bunkodo Co., Ltd., 2016): Daratumumab is reported to be effective also when used alone. A high response rate (36%) was reported in the foreign phase I/II study (Study GEN501) conducted in patients with relapsed or refractory MM and receiving a large number of prior therapies. A longer survival was also reported in responders in the study.

Textbook:

- Williams Hematology, 9th Edition (The McGraw-Hill Companies, Inc., 2016, USA): Daratumumab is expected to be effective, based on data available from the foreign phase I/II study (Study GEN501) conducted in patients with relapsed or refractory MM. Daratumumab is now being studied in combination with Ld.

PMDA's review and discussion:

The clinical benefit of add-on therapy of daratumumab to Ld and Bd has been demonstrated, respectively, in Studies 3003 and 3004 which were conducted in patients with relapsed or refractory MM [see Sections 7.R.2 and 7.R.3]. Based on the findings, PMDA concluded that daratumumab in combination with Ld or Bd can be positioned as a therapeutic option for patients with relapsed or refractory MM. Regarding daratumumab monotherapy, PMDA has concluded that daratumumab monotherapy is not recommended at this time because no clinical study data are available to confirm the clinical benefit of the monotherapy [see Section 7.R.6.4].

7.R.5.2 Intended population and indication of daratumumab

The applicant's explanation of the intended population and the indication of daratumumab:

The patients enrolled in Studies 3003 and 3004 were those who had relapsed or refractory MM and had received at least one prior regimen for MM. In Study 3003, patients who were refractory to or intolerant

41) Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
42) Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
43) Nonconsecutive case series with tumor response rate as an endpoint.

to lenalidomide were excluded. In Study 3004, patients who were refractory to BTZ, ixazomib, or carfilzomib and patients who were intolerant to BTZ were excluded.

PFS results in Studies 3003 and 3004 are shown by the number of prior therapy in Tables 35 and 36, respectively.

Table 35. Results of the interim analysis for PFS (Study 3003, ITT analysis set, central evaluation, data cutoff on March 7, 2016)

Number of prior therapy	Daratumumab/Ld		Ld		Hazard ratio [95%CI]
	N	Median PFS [95%CI] (month)	N	Median PFS [95%CI] (month)	
Overall	286	NE [NE, NE]	283	18.4 [13.9, NE]	0.37 [0.27, 0.52]
1	149	NE [NE, NE]	146	18.4 [14.8 NE]	0.41 [0.26, 0.66]
2	85	NE [NE, NE]	80	11.9 [8.8 NE]	0.29 [0.16, 0.53]
3	38	NE [NE, NE]	38	NE [8.8, NE]	0.36 [0.13, 1.03]
≥4	14	NE [13.2, NE]	19	NE [5.6, NE]	0.53 [0.10, 2.87]

Table36. Results of the interim analysis for PFS (Study 3004, ITT analysis set, central evaluation, data cutoff on January 11, 2016)

Number of prior therapy	Daratumumab/Bd		Bd		Hazard ratio [95%CI]
	N	Median PFS [95%CI] (month)	N	Median PFS [95%CI] (month)	
Overall	251	NE [12.3, NE]	247	7.2 [6.2, 7.9]	0.39 [0.28, 0.53]
1	122	NE [NE, NE]	113	7.5 [6.7, 11.4]	0.31 [0.18, 0.52]
2	70	10.3 [7.4, NE]	74	6.5 [5.7, 8.1]	0.50 [0.28, 0.89]
3	37	8.8 [6.5, 12.3]	32	6.6 [4.2, 8.1]	0.66 [0.31, 1.41]
≥4	22	8.4 [6.5, NE]	28	5.4 [3.8, 6.2]	0.48 [0.20, 1.16]

Since the PFS results by the number of prior therapy in Studies 3003 and 3004 were comparable to those in the overall study population, daratumumab therapy can be recommended for patients with relapsed or refractory MM receiving at least one prior therapy, who were the target population of these studies.

Based on the above, daratumumab was proposed to be indicated for "the treatment of relapsed or refractory multiple myeloma," and the following precautions would be included in the Precautions for Indications section of the package insert.

- Daratumumab should be used in patients with MM who failed to respond to at least one prior standard therapy or who had relapsed MM after the therapy.
- Physicians should select appropriate patients after thoroughly understanding the details of the clinical study patients, including previous treatment history, described in the Clinical Studies section of the package insert and fully understanding the efficacy and safety profiles of daratumumab.

PMDA accepted the applicant's explanation.

7.R.6 Dosage and administration

The Dosage and Administration and Precautions for Dosage and Administration sections of the package insert had been proposed as shown below.

Dosage and administration

- The usual adult dose is 16 mg/kg of daratumumab (genetical recombination) administered as an intravenous drip infusion according to Method A or Method B.

Method A:

Duration of treatment	Treatment interval
Weeks 1-8	Weekly (total of 8 doses)
Weeks 9-24[1)]	Every 2 weeks (total of 8 doses)
Week 25 onwards[2), 3)]	Every 4 weeks

1) First dose of the every-2-week dosing schedule is given at Week 9.
2) First dose of the every-4-week dosing schedule is given at Week 25.
3) Treatment from Week 25 onwards is continued until disease progression.

Method B:

Duration of treatment	Treatment interval
Weeks 1-9	Weekly (total of 9 doses)
Weeks 10-24[1)]	Every 3 weeks (total of 5 doses)
Week 25 onwards[2), 3)]	Every 4 weeks

1) First dose of the every-3-week dosing schedule is given at Week 10.
2) First dose of the every-4-week dosing schedule is given at Week 25.
3) Treatment from Week 25 onwards is continued until disease progression.

Precautions for Dosage and Administration

- Physicians should select chemotherapy including daratumumab based on the patient's condition and prior chemotherapy history after being familiar with information described in the Clinical Studies section of the package insert.
- When daratumumab is used in combination with other anticancer drugs, physicians should thoroughly and carefully read the package inserts of the combination drugs.
- Administration of corticosteroids, antipyretic analgesics, antihistamines, and other drugs used to reduce infusion reactions.
- Infusion rate and total volume after dilution for daratumumab administration.
- Measures to be taken for infusion reactions.

As a result of its review shown below and in Sections "7.R.2 Efficacy" and "7.R.3 Safety," PMDA has concluded that the Dosage and Administration and Precautions for Dosage and Administration sections should include the following statements.

Dosage and administration

When used in combination with other anticancer drugs, the usual adult dose is 16 mg/kg of daratumumab (genetical recombination) administered as an intravenous drip infusion. Depending on the treatment cycle of the concomitant anticancer drug, daratumumab is administered weekly (Weeks 1-8), every 2 weeks (Weeks 9-24), and every 4 weeks (Week 25 onwards) or weekly (Weeks 1-9), every 3 weeks (Weeks 10-24), and every 4 weeks (Week 25 onwards).

Precautions for Dosage and Administration

- The efficacy and safety of daratumumab as monotherapy have not been established.
- Physicians should carefully select the treatment interval of daratumumab and the nature and type of anticancer drugs to be used concomitantly with daratumumab after being familiar with information described in the Clinical Studies section of the package insert. Physicians also should thoroughly and carefully read the package inserts of the concomitant drugs.

- Corticosteroids, antipyretic analgesics, and antihistamines should be administered 1 to 3 hours before the infusion of daratumumab to reduce infusion reactions. Corticosteroids or other proper drugs should be administered as needed after the infusion of daratumumab to reduce delayed infusion reactions. For patients with chronic obstructive pulmonary disease or bronchial asthma or patients with a history of chronic obstructive pulmonary disease or bronchial asthma, physicians should consider prescribing post-infusion medications such as bronchodilators and inhaled corticosteroids.
- Daratumumab should be diluted with normal saline to the total volume of 1,000 mL and should be administered as an intravenous drip infusion at an initial rate of 50 mL/hour. When no infusion reactions occur, the total volume after dilution and infusion rate can be adjusted, as shown below, while the patient's condition is monitored. The maximum infusion rate is 200 mL/hour.

Total volume after dilution and infusion rate for daratumumab administration

Timing of infusion	Total volume after dilution	Infusion rate after the start of administration (mL/h)			
		0-1 h	1-2 h	2-3 h	≥3 h
First infusion	1,000 mL	50	100	150	200
Second infusion	500 mL*1				
Third and subsequent infusions	500 mL*1	100*2	150	200	

*1 In the absence of infusion reactions within 3 hours after the start of the first infusion, use dilution volume of 500 mL.
*2 In the absence of infusion reactions during the first and second infusions with the final infusion rate of ≥100 mL/h, the infusion rate can be started at 100 mL/h.

- In the occurrence of infusion reactions, physicians should take appropriate measures, including interruption, discontinuation, or infusion rate modification of daratumumab, as outlined below. The grades are determined based on the criteria of the NCI-CTCAE version 4.0.
  - Grade 1 to 3: Interrupt daratumumab. Once infusion reaction symptoms resolve, daratumumab can be resumed at no more than half the rate at which the reaction occurred. If the patient does not experience additional infusion reaction, infusion rate can be modified [see above table "Total volume after dilution and infusion rate for daratumumab administration"]. Daratumumab should be permanently discontinued upon the third occurrence of a Grade 3 infusion reaction.
  - Grade 4: Permanently discontinue daratumumab.

7.R.6.1 Dosage and administration of daratumumab

The applicant's explanation of the rationale for the proposed dosage and administration of daratumumab:
In Study GEN501 conducted in patients with relapsed or refractory MM to examine daratumumab as monotherapy, no obvious differences in the safety profiles were observed among patients receiving daratumumab at >4 mg/kg, and it was demonstrated that daratumumab was well tolerated when intravenously administered at 16 mg/kg as a single dose, followed by a 3-week resting period, and then administered weekly in Weeks 4 to 9, every 2 weeks in Weeks 10 to 22, and every 4 weeks in Week 24 and subsequent weeks.

In Study GEN503 conducted in patients with relapsed or refractory MM, the duration of a cycle in Phase I part was set to 28 days which is the same as that for Ld. Daratumumab 2, 4, 8, or 16 mg/kg in combination with Ld was intravenously administered weekly in Cycles 1 and 2, every 2 weeks in Cycles 3 to 6, and every 4 weeks in Cycle 7 and subsequent cycles. Since no DLT was observed with this regimen, it was decided that daratumumab 16 mg/kg was to be administered with the same regimen in Study 3003 as that in Study GEN503.

In Study 3004 conducted in patients with relapsed or refractory MM, in consideration of Bd treatment cycle, the duration of a cycle in Cycles 1 to 8 was set to 21 days, and the duration of Cycle 9 and subsequent cycles was set to 28 days. Daratumumab 16 mg/kg was intravenously administered weekly in Cycles 1 to 3 and every 3 weeks in Cycles 4 to 8 in combination with Bd. In Cycles 9 and subsequent cycles, after completion of concomitant use of Bd, daratumumab 16 mg/kg monotherapy was intravenously administered every 4 weeks.

In Studies 3003 and 3004 conducted with the above design, the clinical benefit of daratumumab was demonstrated in patients with relapsed or refractory MM [see Sections 7.R.2 and 7.R.3]. The proposed dosage and administration of daratumumab were based on these studies.

PMDA accepted the applicant's explanation.

7.R.6.2 Dose adjustment for daratumumab

The applicant's explanation on the dose adjustment for daratumumab:
In Studies 3003 and 3004, criteria for interruption, resumption, and discontinuation of daratumumab were defined and followed, and daratumumab was tolerated. No criteria were specified for dose reduction.

Based on the above, the Precautions for Dosage and Administration section of the package insert were proposed on the basis of the instructions for interruption, resumption, and discontinuation of daratumumab in Studies 3003 and 3004. However, the interruption and resumption criteria specified in Studies 3003 and 3004, except for measures taken for infusion reactions [see Section 7.R.3.3], were not included in the proposed instructions in the Precautions for Dosage and Administration section of the package insert for the following reasons.

- In Studies 3003 and 3004, it was specified that daratumumab was to be interrupted when any of the following events (a) to (d) shown below occurred and when the event was possibly related to factors other than lenalidomide (in Study 3003) or BTZ and DEX (in Study 3004). However, since daratumumab is a drug used by physicians with sufficient experience and expertise, it was decided that instructions concerning these events were not included in the proposed package insert.
  (a) Febrile neutropenia and neutropenia with infections
  (b) Grade 4 hematological toxicity

(c) Thrombocytopenia with ≥Grade 3 bleeding
(d) ≥Grade 3 nonhematological toxicity[44)]

- In Studies 3003 and 3004, it had been specified that daratumumab would be resumed when the adverse event described in the above (a) to (d) resolved to ≤Grade 2. However, instructions for interruption was not mentioned as shown above, and accordingly, instructions for resumption were not mentioned.

PMDA's review and discussion:
PMDA generally accepted the applicant's explanation. However, PMDA concluded that information on the criteria for dose adjustment including those for concomitant drugs specified in Studies 3003 and 3004 should be appropriately provided to healthcare professionals in clinical practice, by means of materials, in addition to the above proposed instructions in the Precautions for Dosage and Administration section.

7.R.6.3 Anticancer drugs concomitantly used with daratumumab

PMDA asked the applicant to explain the concomitant use of daratumumab and anticancer drugs other than Ld and Bd.

The applicant's explanation about the concomitant use of daratumumab and anticancer drugs other than Ld and Bd:
Daratumumab is an antibody drug and reacts with the epitope on the extracellular region of CD38 which is highly expressed in MM patients. Daratumumab has a mechanism of action different from that of other existing anticancer drugs approved for treatment in patients with MM. Daratumumab is thus expected to be clinically useful even when used in combination with anticancer drugs other than Ld and Bd. Therefore, there is no need to restrict the anticancer drugs concomitantly used with daratumumab by dosage and administration.

However, the clinical usefulness of daratumumab in patients with relapsed or refractory MM has not been demonstrated when daratumumab is used in combination with anticancer drugs other than Ld or Bd. Accordingly, a combination of daratumumab with anticancer drugs other than Ld or Bd is not strongly recommended in patients with relapsed or refractory MM at present. In consideration of the above, we proposed to describe in the Clinical Studies section of the package insert that Ld and Bd were the anticancer drugs concomitantly used with daratumumab in Studies 3003 and 3004 and that precautionary statement should be included in the Precautions for Dosage and Administration section of the package insert, stating that physicians should select anticancer drugs for the concomitant use with daratumumab after being familiar with information described in the Clinical Studies section of the package insert.

[44)] Grade 3 nausea or vomiting responding antiemetics, Grade 3 diarrhoea responding to antidiarrheals, and Grade 3 fatigue or asthenia lasting for <7 days after the last daratumumab infusion were excluded.

PMDA's review and discussion:
Considering that daratumumab is an anticancer drug used by physicians with sufficient experience and expertise for the treatment of hematopoietic malignancies, PMDA thinks that the above applicant's explanation is acceptable.

Meanwhile, PMDA concluded that it is appropriate to mention the use of daratumumab in combination with other anticancer drugs in the Dosage and Administration section of the package insert, in light of the following findings: 1) the clinical usefulness of daratumumab in combination of Ld or Bd was demonstrated in Studies 3003 and 3004; and 2) daratumumab monotherapy is not recommended [see Section 7.R.6.4]. Since it should be clearly stated that the treatment interval of daratumumab is chosen based on the treatment cycle of the anticancer drug to be concomitantly used, PMDA has concluded that anticancer drugs used in Studies 3003 and 3004 should be mentioned in the Clinical Studies section and that the following precautions should be included in the Precautions for Dosage and Administration section in the package insert.

- Physicians should carefully select the treatment interval of daratumumab and the nature and type of anticancer drugs to be used concomitantly with daratumumab after being familiar with information described in the Clinical Studies section of the package insert. Physicians also should thoroughly and carefully read the package inserts of the concomitant drugs.

7.R.6.4 Daratumumab monotherapy

The applicant's explanation about daratumumab monotherapy:
The efficacy and safety of daratumumab monotherapy in patients with relapsed or refractory MM were evaluated based on data from the foreign studies (Study 2002 and Part 2 of Study GEN501) and the Japanese study (Study 1002).

In Study 2002 and Part 2 of Study GEN501, patients were enrolled if they were refractory to alkylating agents, high-dose chemotherapy in combination with autologous peripheral stem cell transplantation, BTZ, lenalidomide, carfilzomib, or pomalidomide. The number of prior treatment received was 2 to 14 regimens in Study 2002 and 2 to 12 regimens in Part 2 of Study GEN501, and 97.2% (103 of 106) of patients in Study 2002 and 76.2% (32 of 42) of patients in Part 2 of Study GEN501 were refractory to the last therapy prior to the start of these studies. The response rate was 29.2% (31 of 106 patients) and 35.7% (15 of 42 patients) in Study 2002 and Part 2 of Study GEN501, respectively, and all observed adverse events were clinically manageable in both studies. The number of prior treatment, efficacy, and safety in Study 1002 were all comparable to those in Study 2002 and Part 2 of Study GEN501.

Based on the above findings, daratumumab monotherapy is expected to be a new therapeutic option for patients with relapsed or refractory MM with no other therapeutic options.

PMDA's review and discussion:

No data are available from clinical studies confirming the clinical usefulness of daratumumab as monotherapy in patients with relapsed or refractory MM. Thus, PMDA currently considers that daratumumab monotherapy is not recommended for patients with relapsed or refractory MM. Therefore, PMDA concluded that it needs to be clearly stated in the Dosage and Administration section of the package insert that daratumumab should be used in combination with other anticancer drugs [see Section 7.R.6.3]. PMDA also concluded that precautionary statements should be included in the Precautions for Dosage and Administration section that the efficacy and safety of daratumumab as monotherapy have not been established.

7.R.7 Post-marketing investigations

The applicant's explanation on the post-marketing surveillance plan:
A post-marketing surveillance was planned to be conducted in all patients treated with daratumumab to investigate the safety and other profiles of daratumumab in routine clinical practice after the launch.

Infusion reactions, neutropenia, thrombocytopenia, and infections were to be investigated for the safety specification of this surveillance because they occurred frequently in Studies 3003 and 3004 and are adverse events of special interest for daratumumab treatment.

A planned sample size of 300 patients was chosen based on the occurrence of the events, which were to be investigated for the safety specification of this surveillance, in Studies 3003 and 3004.

An observation period of 52 weeks was chosen because the majority of the events to be investigated for the safety specification of this surveillance occurred within the first one year of the daratumumab therapy in Studies 3003 and 3004 with no increase in their incidence in association with the continuation of daratumumab therapy.

PMDA's review and discussion:
In light of the very limited safety data available for daratumumab treatment in Japanese patients, PMDA concluded that a surveillance encompassing all patients treated with daratumumab should be conducted for a certain period after its market launch. In the surveillance, the safety data should be collected in an immediate and unbiased manner, and the available safety information should be provided immediately to healthcare professionals in clinical practice.

Considering the occurrence of adverse events in Japanese and non-Japanese clinical studies, PMDA concluded that infusion reactions, bone marrow depression, and infections should be investigated for the safety specification of this surveillance.

PMDA concluded that the planned sample size and observation period of this surveillance should be discussed in consideration of the occurrence of the above events to be investigated for the safety specification of this surveillance.

7.3 Adverse events reported in clinical studies

Deaths reported in the clinical study data included in the data package submitted for safety evaluation are described in Sections "7.1 Evaluation data" and "7.2 Reference data." Major adverse events other than death are described below.

7.3.1 Japanese phase I study (Study 1002)

Adverse events occurred in all subjects, and their causal relationship to the study drug could not be ruled out in all events. Adverse events with an incidence of ≥40% in each group were lymphopenia in 4 patients (100%) and neutropenia in 2 patients (50.0%) in the 8 mg/kg group and lymphopenia in 5 patients (100%), neutropenia in 5 patients (100%), leukopenia in 3 patients (60%), and pyrexia in 3 patients (60.0%) in the 16 mg/kg group.

Serious adverse events were reported in 1 of 4 patients (25.0%) in the 8 mg/kg group and 2 of 5 patients (40.0%) in the 16 mg/kg group: thrombocytopenia in 1 patient (25.0%) in the 8 mg/kg group and pneumonia in 1 patient (20%), headache in 1 patient (20%), and pyrexia in 1 patient (20.0%) in the 16 mg/kg group. Among the serious adverse events, a causal relationship to the study drug could not be ruled out for pneumonia in 1 patient, headache in 1 patient, and pyrexia in 1 patient in the 16 mg/kg group.

There were no adverse events leading to discontinuation of the study drug.

7.3.2 Japanese phase Ib study (Study 1005)

Adverse events occurred in all subjects, and their causal relationship to the study drug could not be ruled out in all events. Adverse events with an incidence of ≥20% were thrombocytopenia in 7 patients (87.5%), lymphopenia in 5 (62.5%), anaemia in 3 (37.5%), leukopenia in 3 (37.5%), neutropenia in 3 (37.5%), fatigue in 3 (37.5%), hyperglycaemia in 3 (37.5%), dysaesthesia in 3 (37.5%), blood LDH increased in 3 (37.5%), weight decreased in 3 (37.5%), chills in 2 (25.0%), nasopharyngitis in 2 (25.0%), dehydration in 2 (25.0%), hypokalaemia in 2 (25.0%), constipation in 2 (25.0%), diarrhoea in 2 (25.0%), gastritis in 2 (25.0%), hypoxia in 2 (25.0%), and wheezing in 2 (25.0%).

Serious adverse events were reported in 3 of 8 patients (37.5%): herpes zoster in 1 patient (12.5%), nasopharyngitis in 1 (12.5%), and prostate cancer in 1 (12.5%). Among the serious adverse events, a causal relationship to the study drug could not be ruled out for herpes zoster in 1 patient and nasopharyngitis in 1 patient.

An adverse event, prostate cancer, led to discontinuation of the study drug in 1 of 8 patients (12.5%) and its causal relationship to the study drug adverse event was denied.

7.3.3 Global, phase III study (Study 3003)

Adverse events occurred in 278 of 283 patients (98.2%) in the daratumumab/Ld group and 274 of 281 patients (97.5%) in the Ld group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 269 of 283 patients (95.1%) in the daratumumab/Ld group and 233 of 281 patients (82.9%) in the Ld group. Adverse events with an incidence of ≥20% in either group are shown in Table 37.

Table 37. Adverse events with an incidence of ≥20% in either group

SOC PT (MedDRA/J ver.18.0)	Number of patients (%)			
	Daratumumab/Ld N = 283		Ld N = 281	
	All grades	≥Grade 3	All grades	≥Grade 3
Overall adverse events	278 (98.2)	229 (80.9)	274 (97.5)	207 (73.7)
Blood and lymphatic system disorders				
Neutropenia	168 (59.4)	147 (51.9)	121 (43.1)	104 (37.0)
Anaemia	88 (31.1)	35 (12.4)	98 (34.9)	55 (19.6)
Thrombocytopenia	76 (26.9)	36 (12.7)	77 (27.4)	38 (13.5)
Infections and infestations				
Upper respiratory tract infection	90 (31.8)	3 (1.1)	58 (20.6)	3 (1.1)
Nasopharyngitis	68 (24.0)	0	43 (15.3)	0
Gastrointestinal disorders				
Diarrhoea	121 (42.8)	15 (5.3)	69 (24.6)	9 (3.2)
Constipation	83 (29.3)	3 (1.1)	71 (25.3)	2 (0.7)
Nausea	68 (24.0)	4 (1.4)	40 (14.2)	0
General disorders and administration site conditions				
Fatigue	100 (35.3)	18 (6.4)	78 (27.8)	7 (2.5)
Pyrexia	57 (20.1)	5 (1.8)	31 (11.0)	4 (1.4)
Respiratory, thoracic and mediastinal disorders				
Cough	82 (29.0)	0	35 (12.5)	0
Musculoskeletal and connective tissue disorders				
Muscle spasms	73 (25.8)	2 (0.7)	52 (18.5)	5 (1.8)

Serious adverse events were reported in 138 of 283 patients (48.8%) in the daratumumab/Ld group and 118 of 281 patients (42.0%) in the Ld group. The following serious adverse events occurred in ≥6 patients in each group: in the daratumumab/Ld group, pneumonia in 23 patients (8.1%), febrile neutropenia in 12 (4.2%), influenza in 8 (2.8%), pyrexia in 8 (2.8%), lower respiratory tract infection in 7 (2.5%), and pulmonary embolism in 7 (2.5%); and in the Ld group, pneumonia in 24 patients (8.5%), pulmonary embolism in 8 (2.8%), acute renal failure in 8 (2.8%), and diarrhoea in 6 (2.1%). Among these events, a causal relationship to the study drug could not be ruled out for pneumonia in 15 patients, febrile neutropenia in 12, pulmonary embolism in 7, lower respiratory tract infection in 5, pyrexia in 3, and influenza in 2 in the daratumumab/Ld group and pneumonia in 9, pulmonary embolism in 8, diarrhoea in 3, and acute renal failure in 2 in the Ld group.

Adverse events led to discontinuation of the study drug in 38 of 283 patients (13.4%) in the daratumumab/Ld group and 36 of 281 patients (12.8%) in the Ld group. There was no adverse event that led to discontinuation of the study drug occurring in ≥6 patients in individual groups.

7.3.4 Foreign phase I/II study (Study GEN501)

Adverse events occurred in 31 of 32 patients (96.9%) in Part 1 and 71 of 72 patients (98.6%) in Part 2. Adverse events for which a causal relationship to the study drug could not be ruled out occurred in 28 of 32 patients (87.5%) in Part 1 and 60 of 72 patients (83.3%) in Part 2. Adverse events with an incidence of ≥20% in each part were proteinuria in 15 patients (46.9%) and pyrexia in 11 patients (34.4%) in Part 1 and fatigue in 32 patients (44.4%), nasopharyngitis in 23 patients (31.9%), rhinitis allergic in 22 patients (30.6%), pyrexia in 22 patients (30.6%), upper respiratory tract infection in 19 patients (26.4%), back pain in 17 patients (23.6%), cough in 17 patients (23.6%), dyspnoea in 15 patients (20.8%), and diarrhoea in 15 patients (20.8%) in Part 2.

Serious adverse events occurred in 12 of 32 patients (37.5%) in Part 1 and 28 of 72 patients (38.9%) in part 2. Serious adverse events occurring in ≥2 patients in each part were pyrexia in 3 patients (9.4%) and bronchospasm in 2 patients (6.3%) in Part 1 and pneumonia in 6 patients (8.3%), crossmatch incompatible in 3 patients (4.2%), pyrexia in 3 patients (4.2%), and herpes zoster in 2 patients (2.8%) in Part 2. Among these events, a causal relationship to the study drug was not ruled out for bronchospasm in 2 patients in Part 1 and crossmatch incompatible in 3 patients, herpes zoster in 2 patients, and pneumonia in 1patient in Part 2.

Adverse events led to discontinuation of the study drug in 5 of 32 patients (15.6%) in Part 1 and 1 of 72 patients (1.4%) in Part 2. An adverse event leading to discontinuation of the study drug in ≥2 patients in each part was bronchospasm in 2 patients (6.3%) in Part 1, and a causal relationship to the study drug could not be ruled out for the events.

7.3.5 Foreign phase II study (Study 2002)

Adverse events occurred in all subjects. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 14 of 18 patients (77.8%) in the 8 mg/kg group and 84 of 106 patients (79.2%) in the 16 mg/kg group. Adverse events occurring with an incidence of ≥30% are shown in Table 38.

Table 38. Adverse events with an incidence of ≥30% in either group

SOC PT (MedDRA/J ver.18.0)	Number of patients (%)			
	8 mg/kg N = 18		16 mg/kg N = 106	
	All grades	≥Grade 3	All grades	≥Grade 3
Overall adverse events	18 (100)	11 (61.1)	106 (100)	71 (67.0)
General disorders and administration site conditions				
Fatigue	6 (33.3)	0	43 (40.6)	3 (2.8)
Chills	6 (33.3)	1 (5.6)	10 (9.4)	0
Gastrointestinal disorders				
Nausea	4 (22.2)	1 (5.6)	34 (32.1)	0
Blood and lymphatic system disorders				
Anaemia	9 (50.0)	4 (22.2)	39 (36.8)	25 (23.6)
Thrombocytopenia	6 (33.3)	4 (22.2)	28 (26.4)	20 (18.9)
Respiratory, thoracic and mediastinal disorders				
Cough	6 (33.3)	0	27 (25.5)	0
Metabolism and nutrition disorders				
Hyponatraemia	6 (33.3)	3 (16.7)	7 (6.6)	0
Investigations				
Blood creatinine increased	7 (38.9)	0	10 (9.4)	2 (1.9)
Vascular disorders				
Hypertension	8 (44.4)	4 (22.2)	12 (11.3)	6 (5.7)

Serious adverse events were reported in 6 of 18 patient (33.3%) in the 8 mg/kg group and 33 of 106 patients (31.1%) in the 16 mg/kg group. Serious adverse events occurring in ≥2 patients in each group were general physical health decreased in 5 patients (4.7%), pneumonia in 4 (3.8%), hypercalcaemia in 4 (3.8%), lobar pneumonia in 2 (1.9%), musculoskeletal chest pain in 2 (1.9%), and anaemia in 2 (1.9%) in the 16 mg/kg group. A causal relationship to the study drug was not ruled out for pneumonia in 2 patients, lobar pneumonia in 2 patients, and anaemia in 1 patient.

Adverse events led to discontinuation of the study drug in 5 of 106 patients (4.7%) in the 16 mg/kg group. An adverse event leading to discontinuation of the study drug in ≥2 patients was general physical health decreased in 2 patients (1.9%), and the causal relationship to the study drug was considered unrelated in both patients.

7.3.6 Foreign phase III study (Study 3004)

Adverse events occurred in 240 of 243 patients (98.8%) in the daratumumab/Bd group and in 226 of 237 patients (95.4%) in the Bd group. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 225 of 243 patients (92.6%) in the daratumumab/Bd group and in 196 of 237 patients (82.7%) in the Bd group. Adverse events with an incidence of ≥20% in either group are shown in Table 39.

Table 39. Adverse events with an incidence of ≥20% in either group

SOC PT (MedDRA/J ver.18.0)	Number of patients (%)			
	Daratumumab/Bd N = 243		Bd N = 237	
	All grades	≥Grade 3	All grades	≥Grade 3
Overall adverse events	240 (98.8)	185 (76.1)	226 (95.4)	150 (63.3)
Blood and lymphatic system disorders				
Thrombocytopenia	143 (58.8)	110 (45.3)	104 (43.9)	78 (32.9)
Anaemia	64 (26.3)	35 (14.4)	74 (31.2)	38 (16.0)
Infections and infestations				
Upper respiratory tract infection	60 (24.7)	4 (1.6)	43 (18.1)	2 (0.8)
Nervous system disorders				
Peripheral sensory neuropathy	115 (47.3)	11 (4.5)	89 (37.6)	16 (6.8)
Gastrointestinal disorders				
Diarrhoea	77 (31.7)	9 (3.7)	53 (22.4)	3 (1.3)
General disorders and administration site conditions				
Fatigue	52 (21.4)	11 (4.5)	58 (24.5)	8 (3.4)
Respiratory, thoracic and mediastinal disorders				
Cough	58 (23.9)	0	30 (12.7)	0

Serious adverse events were reported in 102 of 243 patients (42.0%) in the daratumumab/Bd group and in 80 of 237 patients (33.8%) in the Bd group. Serious adverse events occurring in ≥5 patients in each group were pneumonia in 19 patients (7.8%), anaemia in 8 patients (3.3%), thrombocytopenia in 6 patients (2.5%), bronchitis in 5 patients (2.1%), and atrial fibrillation in 5 patients (2.1%) in the daratumumab/Bd group and pneumonia in 22 patients (9.3%) in the Bd group. A causal relationship to the study drug could not be ruled out for pneumonia in 10 patients, anaemia in 4 patients, thrombocytopenia in 4 patients, bronchitis in 3 patients, and atrial fibrillation in 1patient in the daratumumab/Bd group and pneumonia in 13 patients in the Bd group.

Adverse events led to discontinuation of the study drug in 36 of 243 patients (14.8%) in the daratumumab/Bd group and in 39 of 237 patients (16.5%) in the Bd group. Adverse events leading to discontinuation of the study drug in ≥5 patients in each group were peripheral sensory neuropathy in 5 patients (2.1%) in the daratumumab/Bd group and peripheral sensory neuropathy in 11 patients (4.6%) and neuralgia in 5 patients (2.1%) in the Bd group. Among these events, a causal relationship to the study drug could not be ruled out for peripheral sensory neuropathy in 5 patients in the daratumumab/Bd group and peripheral sensory neuropathy in 10 patients and neuralgia in 4 patients in the Bd group.

7.3.7 Foreign phase I/II study (Study GEN503)

Adverse events occurred in all, and their causal relationship to the study drug could not be ruled out in all events. The following adverse events occurred with an incidence of ≥30% in each phase: in Phase I part, muscle spasms in 10 patients (76.9%), neutropenia in 10 patients (76.9%), diarrhoea in 9 patients (69.2%), fatigue in 8 patients (61.5%), nasopharyngitis in 8 patients (61.5%), constipation in 8 patients (61.5%), oedema peripheral in 6 patients (46.2%), insomnia in 6 patients (46.2%), upper respiratory tract infection in 5 patients (38.5%), thrombocytopenia in 5 patients (38.5%), nausea in 5 patients (38.5%), peripheral sensory neuropathy in 5 patients (38.5%), oedema in 4 patients (30.8%), bone pain in 4 patients (30.8%), cough in 4 patients (30.8%), and headache in 4 patients (30.8%); in Phase II part,

neutropenia in 27 patients (84.4%), cough in 16 patients (50.0%), diarrhoea in 14 patients (43.8%), muscle spasms in 14 patients (43.8%), fatigue in 11 patients (34.4%), thrombocytopenia in 10 patients (31.3%), and pyrexia in 10 patients (31.3%).

Serious adverse events were reported in 8 of 13 patients (61.5%) in the Phase I part and 16 of 32 patients (50.0%) in the Phase II part. Serious adverse events occurring in ≥2 patients in each phase were diarrhoea in 2 patients (15.4%) in Phase I part and neutropenia in 3 patients (9.4%), gastroenteritis in 2 patients (6.3%), and pyrexia in 2 patients (6.3%) in Phase II part. Among these events, a causal relationship to the study drug could not be ruled out for diarrhoea in 1 patient in Phase I part and neutropenia in 3 patients in Phase II part.

Adverse events led to discontinuation of the study drug in 2 of 13 patients (15.4%) in Phase I part and 3 of 32 patients (9.4%) in Phase II part: in Phase I part, electrocardiogram QT prolonged in 1 patient (7.7%), neutropenia in 1 patient (7.7%), and thrombocytopenia in 1 patient (7.7%); and in Phase II part, pneumonia viral in 1 patient (3.1%), adenocarcinoma gastric in 1 patient (3.1%), and laryngeal oedema in 1 patient (3.1%). Among these events, a causal relationship to the study drug could not be ruled out for neutropenia in 1 patient and thrombocytopenia in 1 patient in Phase I part and pneumonia viral in 1 patient and laryngeal oedema in 1 patient in Phase II part.

7.3.8 Foreign phase Ib study (Study 1001)

Adverse events occurred in all patients. Adverse events for which a causal relationship to the study drug could not be ruled out were reported in 129 of 133 patients (97.0%). Adverse events occurring with an incidence of ≥30% were neutropenia in 94 patients (70.7%), anaemia in 60 (45.1%), thrombocytopenia in 53 (39.8%), fatigue 52 (39.1%), diarrhoea in 49 (36.8%), constipation in 49 (36.8%), and cough in 41 (30.8%).

Serious adverse events occurred in 54 of 133 patients (40.6%). Serious adverse events occurring in ≥4 patients were pneumonia in 8 patients (6.0%), sepsis in 4 patients (3.0%), febrile neutropenia in 4 patients (3.0%), and fall in 4 patients (3.0%). Among these events, a causal relationship to the study drug could not be ruled out for pneumonia in 4 patients, sepsis in 3 patients, and febrile neutropenia in 3 patients.

Adverse events led to discontinuation of the study drug in 21 of 133 patients (15.8%). There were no adverse events leading to discontinuation of the study drug in ≥3 patients.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

Compliance assessment is now underway, and the results and PMDA's conclusion will be reported in the Review Report (2).

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

Compliance assessment is now underway, and the results and PMDA's conclusion will be reported in the Review Report (2).

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that daratumumab has efficacy in the treatment of patients with relapsed or refractory MM, and that daratumumab has acceptable safety in view of the benefits. Daratumumab is a drug with a new active ingredient. Daratumumab is considered to bind to CD38 expressed on the surface of MM cells and inhibit tumor proliferation by inducing CDC, ADCP, and ADCC in MM cells. Daratumumab provides a new therapeutic option for patients with relapsed or refractory MM, which is of clinical significance. PMDA also considers that clinical positioning, dosage and administration, and post-marketing investigations of daratumumab need to be further investigated.

PMDA has concluded that daratumumab may be approved if daratumumab is not considered to have any particular problems based on comments from the Expert Discussion.

Review Report (2)

August 29, 2017

Product Submitted for Approval

Brand Name	Darzalex Intravenous Infusion 100 mg, Darzalex Intravenous Infusion 400 mg
Non-proprietary Name	Daratumumab (Genetical Recombination)
Applicant	Janssen Pharmaceutical K.K.
Date of Application	December 20, 2016

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

1.1 Efficacy

As a result of discussion in Section "7.R.2 Efficacy" in the Review Report (1), PMDA concluded that the efficacy of daratumumab (genetical recombination) when combined with lenalidomide hydrate (lenalidomide) and dexamethasone (DEX) (hereinafter referred to as "Ld") and daratumumab when combined with bortezomib and DEX (hereinafter referred to as "Bd") has been demonstrated in the global phase III study (Study 54767414MMY3003, hereinafter referred to as Study 3003) and the foreign phase III study (Study 54767414MMY3004, hereinafter referred to as Study 3004) in terms of progression-free survival as the primary endpoint in patients with relapsed or refractory multiple myeloma (MM), because the progression-free survival was significantly prolonged in the daratumumab + Ld group and daratumumab + Bd group as compared with the respective control of Ld group and Bd group.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion above.

1.2 Safety

Based on the results of the review and discussion in Section "7.R.3 Safety" in the Review Report (1), PMDA concluded that infusion reactions, bone marrow depression, infections, and haemolysis should be identified as adverse events of special interest in association with the use of daratumumab.

PMDA also concluded that daratumumab is tolerable when appropriate measures (e.g., follow-up and management of adverse events) are taken by a physician with sufficient knowledge and experience in the treatment of hematopoietic malignancies.

After the preparation of the Review Report (1), the applicant reported that a number of tumor lysis syndrome (TLS) have been identified in the ongoing clinical studies and in the overseas post-marketing data. PMDA thus asked the applicant to provide the latest data on the occurrence of TLS in association with daratumumab therapy.

The applicant's response:
In clinical studies[45] and overseas post-marketing experience (data cutoff date of [redacted]), adverse events under the ICH Standardised MedDRA Queries (SMQ) of "tumour lysis syndrome" (narrow search) were reported in 15 patients (1 patients in Study 3004, 3 patients in the ongoing foreign clinical studies, and 11 patients in the post-marketing experience; all serious), and a causal relationship to daratumumab could not be ruled out in 14 of the 15 patients. TLS led to death in 6 patients[46]) and a causal relationship to daratumumab could not be ruled out in 5 of the 6 patients. Of the 15 patients with TLS, 3 patients met the laboratory criteria for the diagnosis of TLS (*Br J Haematol*. 2004;127:3-11).

PMDA's review and discussion:
Attention should be paid to the occurrence of TLS with the use of daratumumab, because a number of serious TLS, including death, have been reported in the overseas clinical studies and post-marketing setting, and a causal relationship to daratumumab cannot be ruled out. PMDA concluded that data on the occurrence of TLS in clinical studies should be provided to healthcare professionals in clinical practice. PMDA also concluded that precautions on hematological monitoring in patients receiving daratumumab should be properly provided to the healthcare professionals in clinical practice by means of materials including the package insert so that they can take appropriate measures for any abnormalities.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion above.

After the Expert Discussion, the applicant reported that a number of serious anaphylactic reaction as events related to infusion reaction, including death, were reported in the overseas post-marketing setting[47]. PMDA asked the applicant to provide the latest data on the occurrence of anaphylactic reactions after daratumumab infusion.

The applicant's response:
In the ongoing clinical studies and the overseas post-marketing experience (data cutoff date of [redacted]), adverse events under the MedDRA high-level term of "Anaphylactic and anaphylactoid responses" of "anaphylactic reactions" were reported in 11 patients (2 patients in an overseas patient

45) The submitted clinical studies and ongoing clinical studies are included.
46) Primary diseases in patients who died were MM in 3 patients, mantle cell lymphoma in 1 patient, T-cell lymphoma in 1 patient, and unknown in 1 patient.
47) Anaphylactic reaction was not defined as "an adverse event related to infusion reaction" in the data presented in Section "7.R.3.3 Infusion Reactions" of the Review Report (1).

access program and 9 patients in the overseas post-marketing experience[48)]); and anaphylactic reaction was suspected in 3 patients on the basis of their clinical course and other relevant data (1 patient in the overseas patient access program and 2 patients in the overseas post-marketing experience). Anaphylactic reaction resulted in death in 1 patient with cardiac arrest, bronchospasm, and infusion-related reaction, and serious anaphylactic reaction occurred in 8 patients with anaphylactic reaction, 2 patients with anaphylactic shock, 1 patient with anaphylactoid reaction, 1 patient with infusion-related reaction, and 1 patient with bronchospasm and infusion-related reaction. A causal relationship to daratumumab could not be ruled out in all events.

PMDA's review and discussion:
Attention should be paid to the occurrence of anaphylactic reactions as adverse events related to infusion reaction with the use of daratumumab, because a number of serious anaphylactic reactions, including death, have been reported in the overseas post-marketing setting, and a causal relationship to daratumumab in these events cannot be ruled out. PMDA thus concluded that data on the occurrence of infusion reactions including anaphylactic reactions in clinical studies should be provided to healthcare professionals in clinical practice by means of materials such as the package insert.

1.3 Clinical positioning and indication

Based on the results of the review and discussion in Section "7.R.5 Clinical positioning and indication" in the Review Report (1), daratumumab in combination with Ld or Bd can be positioned as a therapeutic option for patients with relapsed or refractory MM. Thus, PMDA concluded that daratumumab should be approved for the proposed indication of treatment of "relapsed or refractory multiple myeloma" after data on prior therapies in patients enrolled in Studies 3003 and 3004 are provided in the Clinical Studies section of the package insert, and precautionary statements shown below are included in the Precautions for Indications section of the package insert. In addition, as a result of a discussion in Section "5.R.1 Use of daratumumab in pregnant or possibly pregnant women and contraception" of the Review Report (1), PMDA concluded that daratumumab should be contraindicated for pregnant or possibly pregnant women.

Precautions for Indications

- Daratumumab should be used in patients with MM who failed to respond to at least one prior standard therapy or who had relapsed MM after the therapy.
- Physicians should select appropriate patients after thoroughly understanding the details of the clinical study patients, including previous treatment history, described in the Clinical Studies section of the package insert and fully understanding the efficacy and safety profiles of daratumumab.

At the Expert Discussion, the expert advisors made comments in support of the PMDA's conclusion above and also made the following comment.

48) The number includes a subject with non-small cell lung cancer who was mistakenly administered.

- No reproductive and developmental toxicity studies have been conducted for daratumumab, and a risk of reproductive and developmental toxicity of daratumumab remains unclear. In principle, therefore, daratumumab should not be used in pregnant or possibly pregnant women. However, the use of daratumumab in these patients should be allowed with the condition that appropriate precautions are provided, considering the following: 1) there has been no report suggesting a risk of teratogenicity of daratumumab so far; and 2) anticancer drugs available for pregnant or possibly pregnant women with MM are very limited.

PMDA's review and discussion:
PMDA considers that the use of daratumumab is not recommended for pregnant or possibly pregnant women because the reproductive and developmental toxicity of daratumumab remains unclear (see Section 5.R.1 of the Review Report (1)). However, in light of the above discussion at the Expert Discussion and the clinical usefulness of daratumumab, PMDA has concluded that the use of daratumumab is acceptable in these patients on the condition that the following should be appropriately addressed. PMDA also has concluded that the applicant should continue to collect data on potential reproductive and developmental toxicity of daratumumab after its market launch and should provide new findings, if any, to healthcare professionals in clinical practice.

- Patients should be selected appropriately and carefully by physicians with sufficient experience and expertise for treatment of hematopoietic malignancies.
- When considered medically necessary for pregnant or possibly pregnant women, daratumumab should be used only for patients in whom the benefits of treatment outweigh the risks.
- Prior to treatment with daratumumab, patients or their family should be sufficiently informed of the facts that no reproductive and developmental toxicity studies have been conducted for daratumumab and that a risk of reproductive and developmental toxicity of daratumumab remains unclear. Consent from patients or their family is obtained for daratumumab treatment.

Based on the above, PMDA instructed the applicant to include the above statements in the Indications, Precautions for Indications, and Use in Pregnant, Parturient and Nursing Women sections of the package insert. The applicant agreed to take such action.

1.4 Dosage and administration

As a result of the review in Section "7.R.6 Dosage and administration" in the Review Report (1), PMDA concluded that the precautions shown below should be included in the Precautions for Dosage and Administration section of the package insert and that the dosage and administration of daratumumab should be stated in the package insert as follows: "When used in combination with other anticancer drugs, the usual adult dose is 16 mg/kg of daratumumab (genetical recombination) administered as an intravenous drip infusion. Depending on the treatment cycle of the concomitant anticancer drug, daratumumab is administered weekly (Weeks 1-8), every 2 weeks (Weeks 9-24), and every 4 weeks (Week 25 onwards) or weekly (Weeks 1-9), every 3 weeks (Weeks 10-24), and every 4 weeks (Week 25 onwards).

Precautions for Dosage and Administration

- The efficacy and safety of daratumumab as monotherapy have not been established.
- Physicians should carefully select the treatment interval of daratumumab and the nature and type of anticancer drugs to be used concomitantly with daratumumab after being familiar with information described in the Clinical Studies section of the package insert. Physicians also should thoroughly and carefully read the package inserts of the concomitant drugs.
- Corticosteroids, antipyretic analgesics, and antihistamines should be administered 1 to 3 hours before the infusion of daratumumab to reduce infusion reactions. Corticosteroids or other proper drugs should be administered as needed after the infusion of daratumumab to reduce delayed infusion reactions. For patients with chronic obstructive pulmonary disease or bronchial asthma or patients with a history of chronic obstructive pulmonary disease or bronchial asthma, physicians should consider prescribing post-infusion medications such as bronchodilators and inhaled corticosteroids.
- Daratumumab should be diluted with normal saline to the total volume of 1,000 mL and should be administered as an intravenous drip infusion at an initial rate of 50 mL/hour. When no infusion reactions occur, the total volume after dilution and infusion rate can be adjusted, as shown below, while the patient's condition is monitored. The maximum infusion rate is 200 mL/hour.

Total volume after dilution and infusion rate for daratumumab administration

Timing of infusion	Total volume after dilution	Infusion rate after the start of administration (mL/h)			
		0-1 h	1-2 h	2-3 h	≥3 h
First infusion	1,000 mL	50	100	150	200
Second infusion	500 mL*1				
Third and subsequent infusions	500 mL*1	100*2	150	200	

*1 In the absence of infusion reactions within 3 hours after the start of the first infusion, use dilution volume of 500 mL.
*2 In the absence of infusion reactions during the first and second infusions with the final infusion rate of ≥100 mL/h, the infusion rate can be started at 100 mL/h.

- In the occurrence of infusion reactions, physicians should take appropriate measures, including interruption, discontinuation, or infusion rate modification of daratumumab, as outlined below. The grades are determined based on the criteria of the NCI-CTCAE version 4.0.
  - Grade 1 to 3: Interrupt daratumumab. Once infusion reaction symptoms resolve, daratumumab can be resumed at no more than half the rate at which the reaction occurred. If the patient does not experience additional infusion reaction, infusion rate can be modified [see above table "Total volume after dilution and infusion rate for daratumumab administration"]. Daratumumab should be permanently discontinued upon the third occurrence of a Grade 3 infusion reaction.
  - Grade 4: Permanently discontinue daratumumab.

At the Expert Discussion, the expert advisors made comments in support of the PMDA's conclusion above and also made the following comment.

- Daratumumab monotherapy is not recommended. The use of daratumumab in combination with Ld

(Combination regimen 1) or Bd (Combination regimen 2) is recommended. The treatment interval of daratumumab differs between the Combination regimens 1 and 2, and the sense can be conveyed to some extent by the wording proposed by PMDA for the descriptions used in the Dosage and Administration and Precautions for Dosage and Administration sections. However, wording should be more clearly used for the precautions describing the relationship of the dosing cycles of daratumumab and the concomitant anticancer drug to avoid confusion in clinical practice.

PMDA's review and discussion:
Based on the above discussion at the Expert Discussion, and in light of the fact that daratumumab is a drug with a new active ingredient and a new mechanism of action, PMDA concluded to clearly describe the relationship of the dosing cycles of daratumumab and the concomitant anticancer drug, the dosage and administration of daratumumab should be specified in the package insert as shown below.

Dosage and Administration
The usual adult dose is 16 mg/kg of daratumumab (genetical recombination) administered as an intravenous drip infusion according to the following dosing schedule.
In combination with lenalidomide and dexamethasone,
Weekly (Weeks 1-8), every 2 weeks (Weeks 9-24), and every 4 weeks (Week 25 onwards)
In combination with bortezomib and dexamethasone,
Weekly (Weeks 1-9), every 3 weeks (Weeks 10-24), and every 4 weeks (Week 25 onwards)

Based on the above, PMDA instructed the applicant to include the above statements in the Dosage and Administration and Precautions for Dosage and Administration sections of the package insert. The applicant agreed to take such action.

1.5 Risk management plan (draft)

The applicant plans to conduct a post-marketing surveillance to evaluate the safety and other profiles of daratumumab in post-marketing clinical practice. The surveillance is planned to cover all patients treated with daratumumab with a target sample size of 300 and an observation period of 52 weeks.

As a result of the review described in Section "7.R.7 Post-marketing investigations" of the Review Report (1), PMDA concluded that an all-case surveillance should be performed in patients receiving daratumumab for a certain period after its market launch, that the safety data should be collected in an prompt and unbiased manner, and that the available safety information should be provided to healthcare professionals in clinical practice without delay. PMDA also reached the following conclusion on the surveillance plan:

- Safety specification of the surveillance should include infusion reactions, bone marrow depression, and infections;

- The target sample size and the observation period should be re-examined and determined on the basis of the occurrence of the events in clinical studies, which are specified in the safety specification of this surveillance.

At the Expert Discussion, the expert advisors supported the PMDA's conclusion above.

Based on the above review, PMDA instructed the applicant to re-examine the surveillance plan.

The applicant's response:
- The safety specification of this surveillance will include infusion reactions, bone marrow depression, and infections.
- Based on the occurrence of the specified events in clinical studies, no change was needed to the target sample size (300 subjects) or the observation period (52 weeks).

PMDA accepted the applicant's response.

In view of Section "1.2 Safety" and the discussion above, PMDA has concluded that the risk management plan (draft) for daratumumab should include the safety and efficacy specifications presented in Table 40 and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Table 41.

Table 40. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Infusion reaction • Bone marrow depression • Infections • TLS • Interference with indirect Coombs test	• Haemolysis	• None
Efficacy specification		
• Efficacy in clinical practice		

Table 41. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified drug use-results survey (all-case surveillance) • Post-marketing clinical study (an extension study of Study 54767414MMY1005) • Post-marketing clinical study (an extension study of Study 3003)	• Provision of information obtained from the early post-marketing phase vigilance • Preparation and distribution of materials for healthcare professionals (including prescribing physicians and blood transfusion divisions) • Preparation and distribution of materials for patients

Table 42. Outline of post-marketing surveillance (draft)

Objective	To evaluate the safety and other relevant matters of daratumumab in post-marketing clinical setting
Survey method	All-case surveillance
Population	All patients treated with daratumumab
Observation period	52 weeks
Planned sample size	300 patients
Main survey item	Safety specification: infusion reactions, bone marrow depression, and infections. Other main survey items: patient demographics (sex, age, disease stage, concurrent conditions, prior therapies), details of daratumumab therapy, concomitant drugs, adverse events, etc.

1.6 Miscellaneous

1.6.1 Quality of the drug product

PMDA concluded that the quality of the drug product has been properly controlled after confirming that no issue was identified for the quality of the product during the specified shelf-life in stability studies of the drug product.

2. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

2.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection and assessment revealed no noteworthy issues. PMDA thus concluded that there were no obstacles to conducting its review based on the application documents submitted.

2.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1.1-1, 5.3.5.2.3-1, 5.3.5.2.4-1) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics. The inspection revealed that generally the clinical studies were conducted in accordance with the GCP. PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted. Since the following matters were identified at some of the study sites during the inspection, though with no significant impact on the overall evaluation of the studies, PMDA notified the heads of the study sites of the improvement areas.

Improvement areas

Study sites

- Deviation from the protocol (noncompliance with rules for confirmation of the criteria for eligibility at screening, noncompliance with rules for administration methods of the study drug)
- Some subjects did not promptly receive information that would influence their willingness to continue participation in studies.

3. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved after the modification of proposed indication and dosage and administration as shown below, provided that appropriate cautions will be included in the package insert and information concerning the proper use of daratumumab will be provided appropriately after the market launch, and the compliance with the proper use of daratumumab will be ensured under the supervision of physicians with adequate knowledge and experience in hematopoietic malignancies at medical institutions with adequate facilities for the treatment of emergencies. The re-examination period for the product is 10 years since it is designated as an orphan drug. The product is classified as a biological product. Both the drug substance and the drug product are classified as powerful drugs.

Indication

Relapsed or refractory multiple myeloma

Dosage and Administration

The usual adult dose is 16 mg/kg of daratumumab (genetical recombination) administered as an intravenous drip infusion according to the following dosing schedule:
In combination with lenalidomide and dexamethasone,
Weekly (Weeks 1-8), every 2 weeks (Weeks 9-24), and every 4 weeks (Week 25 onwards)
In combination with bortezomib and dexamethasone,
Weekly (Weeks 1-9), every 3 weeks (Weeks 10-24), and every 4 weeks (Week 25 onwards)

Conditions of Approval

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because Japanese data from clinical studies are extremely limited, the applicant is required to conduct a post-marketing use-results survey on all patients until data from a certain number of patients are collected in identifying the characteristics of patients treated with the product, collect data on the safety and efficacy of the product without delay, and take necessary action for the proper use of the drug product.

Warning

Daratumumab should be used only in patients who are considered appropriate to receive daratumumab under the supervision of physicians with adequate knowledge and experience in hematopoietic malignancies at medical institutions with adequate facilities for the treatment of emergencies. Prior to the start of daratumumab, the patient or his/her family should be fully informed about the benefits and risks associated with the treatment. Daratumumab therapy should be started only after consent is obtained from the patient or his/her family.

Contraindications

Patients with a history of hypersensitivity to any of the ingredients of daratumumab.

Precautions for Indications

1. Daratumumab should be used in patients with MM who failed to respond to at least one prior standard therapy or who had relapsed MM after the therapy.
2. Physicians should select appropriate patients after thoroughly understanding the details of the clinical study patients, including previous treatment history, described in the Clinical Studies section of the package insert and fully understanding the efficacy and safety profiles of daratumumab.

Precautions for Dosage and Administration

1. The efficacy and safety of daratumumab as monotherapy have not been established.
2. Physicians should carefully select the treatment interval of daratumumab and the nature and type of anticancer drugs to be used concomitantly with daratumumab after being familiar with information described in the Clinical Studies section of the package insert. Physicians also should thoroughly and carefully read the package inserts of the concomitant drugs.
3. Corticosteroids, antipyretic analgesics, and antihistamines should be administered 1 to 3 hours before the infusion of daratumumab to reduce infusion reactions. Corticosteroids or other proper drugs should be administered as needed after the infusion of daratumumab to reduce delayed infusion reactions. For patients with chronic obstructive pulmonary disease or bronchial asthma or patients with a history of chronic obstructive pulmonary disease or bronchial asthma, physicians should consider prescribing post-infusion medications such as bronchodilators and inhaled corticosteroids.
4. Daratumumab should be diluted with normal saline to the total volume of 1,000 mL and should be administered as an intravenous drip infusion at an initial rate of 50 mL/hour. When no infusion reactions occur, the total volume after dilution and infusion rate can be adjusted, as shown below, while the patient's condition is monitored. The maximum infusion rate is 200 mL/hour.

Total volume after dilution and infusion rate for daratumumab administration

Timing of infusion	Total volume after dilution	Infusion rate after the start of administration (mL/h)			
		0-1 h	1-2 h	2-3 h	≥3 h
First infusion	1,000 mL	50	100	150	200
Second infusion	500 mL*1				
Third and subsequent infusions	500 mL*1	100*2	150	200	

*1 In the absence of infusion reactions within 3 hours after the start of the first infusion, use dilution volume of 500 mL.
*2 In the absence of infusion reactions during the first and second infusions with the final infusion rate of ≥100 mL/h, the infusion rate can be started at 100 mL/h.

5. In the occurrence of infusion reactions, physicians should take appropriate measures, including interruption, discontinuation, or infusion rate modification of daratumumab, as outlined below. The grades are determined based on the criteria of the NCI-CTCAE version 4.0.

1) Grade 1 to 3: Interrupt daratumumab. Once infusion reaction symptoms resolve, daratumumab can be resumed at no more than half the rate at which the reaction occurred. If the patient does not experience additional infusion reaction, infusion rate can be modified [see above table "Total volume after dilution and infusion rate for daratumumab administration"]. Daratumumab should be permanently discontinued upon the third occurrence of a Grade 3 infusion reaction.
2) Grade 4: Permanently discontinue daratumumab.